

AWARD NUMBER: W81XWH-14-C-0048

TITLE: Pupillometry and Saccades as Objective mTBI Biomark

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CONTRACTING ORGANIZATION: The Geneva Foundation
TACOMA WA 98402-4437

REPORT DATE: June 2017

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE June 2017		2. REPORT TYPE Final		3. DATES COVERED 30 Sep 2014 - 29 Mar 2017	
4. TITLE AND SUBTITLE Pupillometry and Saccades as Objective mTBI Biomark				5a. CONTRACT NUMBER W81XWH-14-C-0048	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) LTC Jose E. Capo-Aponte E-Mail: Jose.E.CapoAponte.mil@mail.mil				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Geneva Foundation TACOMA WA 98402-4437				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES mild traumatic brain injury (mTBI), infrared pupillometers, King-Devick (KD) test, near point of convergence (NPC) rule, objective biomarkers					
14. ABSTRACT The objective of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for the identification of Warfighters with acute mild traumatic brain injury (mTBI) using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively. Hundred mTBI and 100 age-matched non-TBI (controls) military personnel were recruited from the patient population at Womack Army Medical Center (WAMC). This study was designed to determine within each group the effectiveness of these tests, individually and/or in combination, to correctly identify mTBI in agreement with the mTBI diagnosis made by the WAMC Department of Brain Injury Medicine. Results showed that three of the eight PLR parameters are statistically different between the groups: average constriction velocity, average dilation velocity, and 75% dilation recovery time. In addition, the KD test, NPC rule, and the CISS survey showed sensitivity in identifying military personnel with mTBI.					
15. SUBJECT TERMS Nothing listed					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 77	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Accomplishments.....	4
4. Impact.....	8
5. Changes/Problems.....	8
6. Products.....	9
7. Participants & Other Collaborating Organizations.....	9
8. Special Reporting Requirements.....	11
9. Appendices.....	11

INTRODUCTION:

The DOD reported that 333,169 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.4% (DVBIC 2015). The diagnosis of mTBI has been a challenge for the military primarily because of the lack of objective assessment tools, overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD), and the interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters (Marion 2011). The objective of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for the identification of Warfighters with acute mTBI using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively. Hundred acute mTBI (≤ 72 hrs post injury) and 100 age-matched non-TBI (controls) military personnel will be recruited from the patient population at Womack Army Medical Center (WAMC). This study was designed to determine within each group the effectiveness of these tests, individually and/or in combination, to correctly identify mTBI in agreement with the mTBI diagnosis made by the WAMC Department of Brain Injury Medicine. There are four hypotheses being tested. First, those who have suffered acute mTBI/concussion will have abnormal PLR findings in comparison to controls. Second, those who have suffered acute mTBI/concussion will have abnormal KD test score in comparison to controls. Third, those who have suffered acute mTBI/concussion will have receded NPC compared to controls. Fourth, those who have suffered acute mTBI/concussion will have higher Convergence Insufficiency Symptoms Survey (CISS) scores in comparison to controls.

KEYWORDS:

pupillometer, pupillary light reflex, PLR, King-Devick test, KD test near point of convergence, convergence insufficiency symptoms surveys, CISS, mild Traumatic Brain Injury, mTBI, military, visual biomarkers, PLR-200, NPi-100.

ACCOMPLISHMENTS:

- **What were the major goals of the project? / What was accomplished under these goals?**

Major Task 1: Administrative Requirements

Subtask 1: Hire Optometrist and Ophthalmic Assistance: COMPLETED

Subtask 2: Purchase equipment and supplies: COMPLETED

Subtask 3: WAMC IRB approval: COMPLETED

Subtask 4: USAMRMC HRPO approval: COMPLETED

Major Task 2: Data Collection on Military Personnel at WAMC

Subtask 1: Procedures and data collection training/standardization: COMPLETED

Subtask 2: Complete data collection in 100 subjects with mTBI: COMPLETED

Subtask 3: Complete data collection in 100 age-matched control subjects (non-TBI): COMPLETED

Major Task 3: Data Analysis and Report Writing

Subtask 1: Complete progress report: COMPLETED

WAMC IRB and USAMRMC HRPO approved the original and subsequent study protocol amendments and continuing reviews. Quarterly reports were submitted throughout Year 1 and Year 2 to Contract Specialist, U.S. Army Medical Research Acquisition Activity and Science Officer, Congressionally Directed Medical Research Programs, USAMRMC, following the timeline indicated in the contract. A 3-month no cost extension was approved and a quarterly report was also submitted at the end of the quarter to the Contract Specialist.

Subtask 2: Complete data analysis: COMPLETED

Population Demographics: Data were included from 100 service members with acute mTBI (87 males, 13 females) and 100 age-matched controls (79 males, 21 females). The mean age was 26 ± 6 years and ranged from 19 to 44 years of age. No significant differences were found between the mTBI group and the age-matched controls on the basis of sex ($p = 0.13$) or race / ethnicity ($p = 0.70$). There was a significant difference in rank between the two groups ($p < 0.001$) with the mTBI group containing fewer officers than were present in the control group. All subjects, in both groups, had normal pupil response and no afferent pupil defect with the manual penlight examination (Appendix I, Table 1).

Injury Characteristics: Thirty one percent of the mTBI group presented to the clinic within 24 hrs, 40% presented within 48 hrs, and 29% presented within 72 hrs. The most common mechanism of injury was airborne training activities (jump), 69%. The remaining injuries were attributed to fall (7%), motor vehicle accident (6%), other (6%), blunt force (5%), sports/recreation (5%), and combative training (2%).

Pupillary Light Reflexes Measured with PLR-200 Pupillometer: There was no statistically significant difference (all $p > 0.05$) for any of the PLR parameters between the right and left eye nor between trials. Therefore, PLR data from trial 1 and 2 for the right and left eye were combined for further between-group comparison. Results indicate that three of the eight PLR parameters are suited to objectively differentiating between normal and mTBI participants (Appendix I, Table 2). The Average Dilation Velocity (ACV) and Average Dilation Velocity (ADV) were slower in the mTBI group ($p < 0.001$, $\eta^2 = 0.07$; and $p < 0.001$, $\eta^2 = 0.30$, respectively). In addition, it took longer for pupils to reach 75% (T75) of pre-stimulated size among the acute mTBI group compare to controls, $p < 0.001$, $\eta^2 = 0.30$.

Pupillary Light Reflexes Measured with NPi-100 Pupillometer: Unlike the PLR-200, the NeuroOptics®NPi™ -100 (NPi-100) pupillometer has a normative database embedded into the instrument and has a unique data point called the Neuro-Pupillary index (NPi). The NPi is based off an algorithm that takes some of the remaining variables inputs and compares them to the normative database to give a composite score pupillary response between 0-5; a value below 3 is considered an abnormal pupillary reflex. Results of the between-group analyses of NPi-100 outcome measures are shown in Table 3, Appendix J. In both eyes, three of the eight outcome measures showed significant differences between the two groups: ACV (right eye: $t(198) = 4.01$, $p < 0.001$; left eye: $t(198) = 4.14$, $p < 0.001$); maximum constriction velocity (MCV) (right eye: $U = 3604$, $p < 0.001$; left eye: $U = 3554$, $p < 0.001$); ADV (right eye: $t(198) = 3.08$, $p = 0.002$; left eye: $t(198) = 3.54$, $p < 0.001$). In the right eye only, percent constriction was significant between the groups ($t(198) = 2.53$, $p = 0.01$). The primary outcome measure of NPi

value was not significantly different between the groups in either eye. Results indicated that though some of the NPi-100 pupillometer secondary outcome measures were significantly different between both groups (i.e., ACV, MCV, ADV), the main outcome measure of NPi was not effective as a biomarker screening parameter. It is worth mentioning that the NPi-100 pupillometer does not calculate 75% recovery (i.e., T75), which was one of the three significant parameters measured with the PLR-200 pupillometer (i.e., ACV, ADV, T75).

Near Point of Convergence: The mean NPC break for the acute mTBI group 13.25 ± 8.07 cm and for the controls was 8.18 ± 2.15 cm. Statistically significant results indicate that the acute mTBI group had receded NPC compared to controls, $p < 0.001$ (Appendix I, Table 3). Based on clinical practice guidelines a scores greater than 10 cm indicated receded convergence. The sensitivity and specificity of the NPC break were 0.81 and 0.49, respectively. This indicates a high number of false positives (51%).

King-Devick Test: The mean KD test completion time for participants in the acute mTBI and controls groups were 60.28 ± 19.50 sec and 44.53 ± 8.05 sec, respectively (Appendix I, Table 3). Statistically significant results indicate that the acute mTBI group took longer to complete the KD test $p < 0.001$ (Appendix I, Table 3). Based on KD test guidelines for injury determination the sensitivity and specificity were 0.45 and 0.92, respectively. This indicates a high number of false negatives (55%).

Convergence Insufficiency Symptoms Survey: The mean CISS score was 24.76 ± 12.06 among participants in the acute phase mTBI group and 8.82 ± 7.42 for the controls. Results indicate that the higher CISS scores for the acute phase mTBI group represent a statistically significant difference, $p < 0.001$ (Appendix I, Table 3). Using the survey cutoff score of 20, the sensitivity and specificity of the CISS were 0.59 and 0.91, respectively. The number of false negatives among the acute mTBI participants closely mirrors the results of the KD test.

Regression Analysis: Binary logistic regression was used to predict injury status (acute phase mTBI or control) using participant's scores on the KD test, NPC, CISS, and PLR parameters (ADV and ACV). A test of the full model was statistically significant, indicating that the predictor variables reliably discriminated between the groups ($p < 0.001$). The resulting Nagelkerke R^2 of 0.71 indicates a moderately strong relationship between the predictor variables and the group variable. Prediction success overall was 87.5% (91.0% for controls and 84.0% for acute phase mTBI participants). Regression coefficients are presented in Appendix I, Table 5 and Figure 4. Receiver operating characteristic (ROC) curve analysis indicates an Area Under the curve (AUC) for the model of 0.93 which indicates very good overall accuracy for the model.

Discussion: The present study validated the use of the PLR (i.e., ACV and ADV) and NPC break as objective biomarkers for acute mTBI. These visual functions can be accurately and quickly measured using instrumentation that is portable, non-invasive, causes no discomfort or risk to patient, minimal training, deployable, commercially available, and relatively low cost. Objective biomarkers, such as these visual function assessment, are needed to assist front-line medical providers in making RTD decisions after a suspected acute mTBI.

However, given the variety of visual deficits resulting from mTBI and the broad range of injury severity within the mTBI category, it is unrealistic to expect that a single visual function can serve as a universal concussion biomarker. This study shows that a combination of visual functions increases the sensitivity to correctly identify acute mTBI than any one test alone.

Results of the present study indicate that the ADV and ACV of the PLR are better suited for discriminating between individuals with and without acute phase mTBI than other commonly used instruments.

Another aim of the study was to investigate validity of the Neuro-Pupillary index (NPi) measured with the NeuroOptics NPi-100 pupillometer since it has a normative database embedded into the instrument. The NPi is based off an algorithm that takes some of the remaining variables inputs and compares them to the normative database to give a composite score pupillary response between 0-5; a value below 3 is considered an abnormal pupillary reflex. Results from the study demonstrated significant differences in ~ 40% of the outcomes measures between the acute mTBI and age-matched control groups (i.e., ACV, MCV, ADV). However, a significant difference between the two study groups was not observed with the NPi value.

Several limitations to the study were identified and should be considered when evaluating the results. The participants were convenience sampled from clinics in a military setting. Therefore, the data cannot be assumed to be representative of the greater civilian population given differences in age, gender distribution, and fitness level. In addition, the majority of acute phase mTBI participants in this study suffered injury after jumping from an airplane, a mechanism of injury not likely to be the primary cause of mTBI in the civilian population. However, this injury modality still represents blunt force trauma to the head and diagnostic criteria for mTBI were similar to those used in civilian populations. Additionally, none of the acute phase mTBI injuries resulted from blast exposure. Consequently, the results of this study cannot be assumed to hold for samples of individuals with blast injuries or polytrauma such as may occur in motor vehicle accidents or assaults. Finally, the instruments used in this study have been demonstrated to be effective screening tools for mTBI during the acute injury phase. However, the ability to assess the severity of injury or provide prognosis information was not evaluated. Thus, while the results of this study can inform injury evaluation in general, no claim can be made regarding the clinical utility of these screening tools for determining injury severity or likely persistence of symptoms and recovery times.

Conclusions: Our findings demonstrate that ADV, ACV (measured with PLR-200 pupillometer), and NPC break are objective visual functions markedly affected in the acute mTBI group compared to controls, and therefore, appear to be useful biomarkers for acute mTBI. The study results also support the added benefit of using vision related subjective instruments, such as the KD test and CISS, in conjunction to abovementioned objective biomarkers, to increase the predictability to identify acute mTBI. In addition, the results indicated that though some of the NPi-100 pupillometer outcome measures were significant between both groups, the NPi value was not effective as a biomarker screening parameter. Thus, while each instrument can accurately differentiate the injury and control groups, results suggest that they differ with regard to their sensitivity and specificity. Where available, objective assessment (i.e., ADV, ACV, and NPC) should be considered preferable to subjective assessments and those based on self-report. Healthcare providers should consider the relative differences of available assessment tools when screening for acute mTBI and consider the use of multiple assessments when feasible to aide in making RTD and return to play determinations or to monitor the recovery of post-concussive syndrome.

Subtask 3: Complete final report: COMPLETED

- **What opportunities for training and professional development has the project provided?**

Nothing to report

- **How were the results disseminated to communities of interest?**

The results of this research were disseminated through the presentation of three poster and four lectures in professional meeting as well as through the publication of two articles in peer reviewed journals. Another article was recently submitted for publication in the Journal Military Medicine.

- **What do you plan to do during the next reporting period to accomplish the goals?**

Nothing to report. This is the final report.

- **What was the impact on the development of the principal discipline(s) of the project?**

The results of this study led to the implementation of PLR, NPC break test, KD test, and CISS survey as part of the assessment tools to confirm and monitor the recovery of TBI-associated visual symptoms for Soldiers undergoing post-concussive vision evaluation and rehabilitation at the Intrepid Spirit Center at Fort Bragg, NC. This will be further implemented at other Intrepid Spirit Centers throughout the nation as part of an ongoing effort to standardization ophthalmic testing.

- **What was the impact on other disciplines?**

Other disciplines can use the battery of tests described in this study as adjunct assessment tools to validate the diagnosis of concussion/mTBI.

- **What was the impact on technology transfer?**

Nothing to Report

- **What was the impact on society beyond science and technology?**

The results of this study are also applicable for civilian population who suffered a concussion resulting from contact sports, motor vehicle accidents, falls, etc. Limitation regarding the extrapolation of the results of this study in other populations were included above under the discussion section.

IMPACT

The validation of these objective tools can facilitate the early identification of Warfighters suspected of suffering a concussion as well as to help monitor the recovery of oculomotor dysfunctions that resulted from mTBI.

CHANGES/PROBLEMS

Nothing to report. This is the final report.

PRODUCTS

- **Journal publications.**

- Appendix H: Article published in the Journal of the Neurological Sciences: Assessment of the King-Devick (KD) test for screening acute mTBI/concussion in warfighters (Sep 2016)
- Appendix I: Article accepted for publication in the Journal Military Medicine: Validation of Visual Objective Biomarkers for Acute Concussion (Feb 2017)
- Appendix J: Another article was submitted for publication in the Journal Military Medicine: Assessment of the NPi-100 Pupillometer test for screening acute mTBI/concussion in Warfighters (Mar 2017)

- **Books or other non-periodical, one-time publications.**

Nothing to Report

- **Other publications, conference papers, and presentations.**

- Appendix A: Lecture at WAMC Annual Research Symposium (May 2015)
- Appendix B: Lecture at the American Academy of Optometry Meeting (Oct 2015)
- Appendix C: Poster at Association of Military Surgeons of the United States Meeting (12 Dec 2015)
- Appendix D: Lecture at WAMC Annual Research Symposium (May 2016)
- Appendix E: Poster at American Optometric Association Meeting (Jul 2016)
- Appendix F: Lecture at American Optometric Association Meeting (Jul 2016)
- Appendix G: Poster at Military Health System Research Symposium (Aug 2016)

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques.**

Nothing to Report

- **Inventions, patent applications, and/or licenses.**

Nothing to Report

- **What was the impact on technology transfer?**

Nothing to Report

- **Other Products?**

Nothing to Report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	LTC Jose E. Capo-Aponte, O.D., Ph.D.
Project Role:	Principal Investigator (PI); Research Optometrist
Nearest person month worked:	12
Contribution to Project:	Provided overall study oversight, protocol development and amendments, ensuring adherence to the protocol, reporting any deviations from protocol, and reports preparation.
Funding Support:	Womack Army Medical Center

Name:	Wesley R. Cole, Ph.D.
Project Role:	Associate Investigator; Neuropsychologist
Nearest person month worked:	3
Contribution to Project:	Assisted with study oversight, protocol and amendments development, ensuring adherence to the protocol, reporting any deviations from protocol, recruiting, informed consent, and reports preparation.
Funding Support:	Defense and Veterans Brain Injury Center (DVBIC)

Name:	LTC David V. Walsh, O.D., Ph.D.
Project Role:	Associate Investigator (PI); Research Optometrist
Nearest person month worked:	4
Contribution to Project:	Provided assistance with protocol development and amendments, data analysis and interpretation and reports preparation.
Funding Support:	US Army Aeromedical Research Laboratory (USAARL)

Name:	Thomas Urosevich, O.D., M.S.
Project Role:	Associate Investigator (PI); Research Optometrist
Nearest person month worked:	1
Contribution to Project:	Provided assistance with data analysis and interpretation and reports preparation.
Funding Support:	Award

Name:	Ashley Ballard, O.D.
Project Role:	Research Optometrist
Nearest person month worked:	14
Contribution to Project:	Assisted with amendments development, ensuring adherence to the protocol, recruiting, informed consent, data collection.
Funding Support:	Award

Name:	Anthony Fioravanti, O.D.
Project Role:	Research Optometrist
Nearest person month worked:	2
Contribution to Project:	Assisted with amendments development, ensuring adherence to the protocol, recruiting, informed consent, data collection.
Funding Support:	Award

Name:	Thomas Beltran, M.S.
Project Role:	Research Assistant
Nearest person month worked:	18
Contribution to Project:	Assisted with recruiting, consenting and data collection.
Funding Support:	Defense and Veterans Brain Injury Center (DVBIC)

Name:	Joseph Dumayas, M.S.
Project Role:	Ophthalmic Assistant; Study Coordinator
Nearest person month worked:	27
Contribution to Project:	Coordinated research activities between team members of the Optometry Department and the Department of Brain Injury Medicine. In addition, conducted recruiting, consenting and data collection.
Funding Support:	Award

Name:	Jacques Arrieux, M.A.
Project Role:	Research Assistant
Nearest person month worked:	1
Contribution to Project:	Assisted with recruiting, consenting and data collection.
Funding Support:	Defense and Veterans Brain Injury Center (DVBIC)

Name:	Stephanie Fonda, Ph.D.
Project Role:	Statistician
Nearest person month worked:	1
Contribution to Project:	Perform data analysis and assist with analysis interpretation
Funding Support:	Award

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to Report

- **What other organizations were involved as partners?**

Organization Name: Defense and Veterans Brain Injury Center (DVBIC)

Location: Womack Army Medical Center

Partner's contribution to the project: Collaboration.

Organization Name: US Army Aeromedical Research Laboratory (USAARL)

Location: Fort Rucker, AL

Partner's contribution to the project: Collaboration.

SPECIAL REPORTING REQUIREMENT

Nothing to Report

APPENDICES:

- Appendix A: Lecture at WAMC Annual Research Symposium (May 2015)
- Appendix B: Lecture at the American Academy of Optometry meeting (Oct 2015)
- Appendix C: Poster at Association of Military Surgeons of the United States annual meeting (12 Dec 2015)
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- Appendix J: Article submitted for publication in the Journal Military Medicine: Assessment of the NPi-100 Pupillometer test for screening acute mTBI/concussion in Warfighters (Mar 2017)

Pupillometry and Saccades as Objective mTBI Biomarker

RIF13R623

W81XWH-14-C-0048



PI: LTC Jose Capo-Aponte, OD, PhD

Org: Womack Army Medical Center/Geneva Foundation

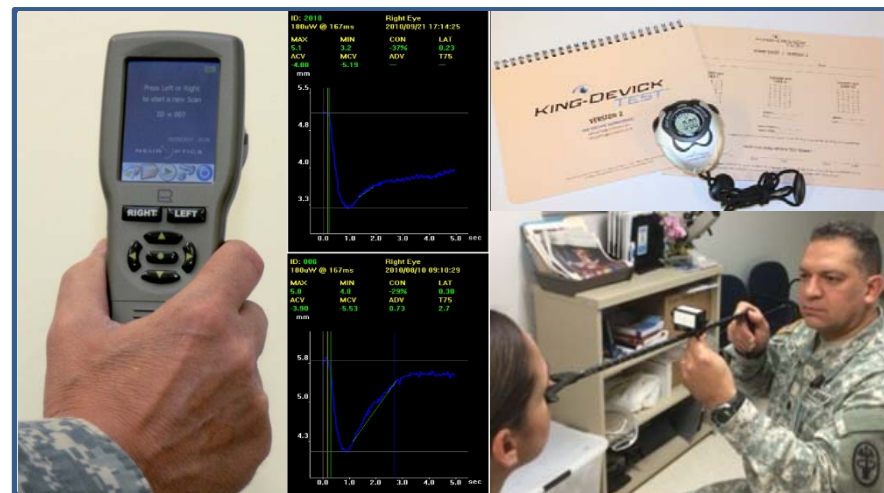
Award Amount: \$491,815

Study/Product Aim(s)

- The DOD reported 333,169 cases of traumatic brain injury (TBI) confirmed since 2000, with 82.4% diagnosed with mild TBI (mTBI)
- mTBI diagnosis is challenging for the military due to lack of objective assessment tools
- The aim of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for identification of Warfighters with acute mTBI using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively.

Approach

100 acute mTBI (≤ 72 hrs post injury) and 100 age-matched non-TBI (controls) military personnel will be recruited from the patient population at Womack Army Medical Center. The study will determine within each group the effectiveness of these COTS tests, individually and/or in combination, to correctly identify patients with mTBI.



Accomplishment: Preliminary results showed 3 of 8 PLR parameters are statistically different between groups: average constriction velocity, average dilation velocity, and 75% dilation recovery time. KD test and NPC are also significantly effected in mTBI group.

Timeline and Cost

Activities	FY	15	16	17
Task 1: Administrative Requirements				
Task 2: Data Collection on Military Personnel at WAMC				
Task 3: Data Analysis and Report Writing				
Estimated Budget (\$K)		\$255.9	\$235.9	NTE

Goals/Milestones

FY15 Goals – Study initiation / Initiate Data collection

- ☒ Hire study staff and purchase equipment/supplies
- ☒ Initial protocol approval by WAMC IRB and MPMC HRPO
- ☒ Enroll 100 mTBI subjects
- ☒ Enroll 100 age-matched non-TBI subjects

FY16 Goals – Cont. Data collection / Data Analysis / Reports

- ☒ Continuing review approval by WAMC IRB and MPMC HRPO
- ☒ Cont. enrollment mTBI
- ☒ Cont. enrollment age-matched non-TBI subjects
- ☒ Data Analysis and Report Writing (in Progress)

Comments/Challenges/Issues/Concerns

- None; Project was completed.

Budget Expenditure to Date

Projected Expenditure: \$491,815

Actual Expenditure: \$354,925.99

Updated: (30 Jun 2017)

Validation of Objective Visual System Biomarkers for Early Identification of Warfighters with Acute mTBI/concussion: Preliminary Results

Dr. Ashley D. Ballard
The Geneva Foundation
Optometrist / Department of Optometry
WAMC, Fort Bragg, NC

Co-Investigators: Thomas A Beltran; LTC Jose E. Capo-Aponte;
Dr. Wesley R. Cole; Joseph Y. Dumayas; MAJ David V. Walsh



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Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Funded by US Army Medical Research and Materiel Command (USAMRMC), FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP). Award # W81XWH-14-C-0048.



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Introduction

- The DOD reported that 320,344 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.5%.
- The diagnosis of mTBI has been a challenge for the military primarily because of the lack of objective assessment tools, overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD), and the interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters.
- Prompt and accurate diagnosis and management of mTBI generally increases an individual's prognosis for neurological recovery and safe return to duty (RTD).
- Premature RTD places Warfighters at greater risk of disability if they suffer an additional concussive trauma. Consequently, there is a quest for objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.



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Introduction

Gaps

- Lack of objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.
- Ideal devices are: accurate, quick to perform, non-invasive, causes no discomfort or risk to patient, minimal training, deployable, low cost.
- Valid objective markers are particularly important in the theater to assist deployed clinicians to make an accurate determination of fit-for-duty (FFD)/RTD or evacuation.

Objectives

- Since approximately 30 areas of the brain, and 7 of the 12 cranial nerves deal with vision, it is not unexpected that the patient with TBI may manifest a host of visual problems, such as pupillary deficit, visual processing delays, and impaired oculomotor tracking and related oculomotor-based reading dysfunctions.
- The proposed study will investigate pupillometry, version (i.e., saccades) and vergence (i.e., convergence) eye movements as potential objective biomarkers for acute mTBI.
- We have included 3 eye procedures and 1 questionnaire in this study (10 min).



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Methods

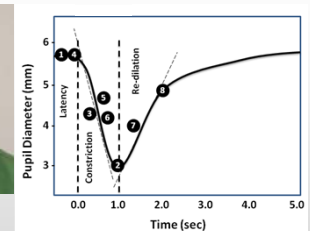
- Case-Control Correlational Design
- Approved for 200 AD military personnel aged matched
 - Preliminary data 125 subjects
 - 91 mTBI; age 19-44
 - 34 Non-TBI; age 29-44
- Pupillometry (NeuroOptics PLR-200) x2
- Vergence Eye Movement (NPC ruler) x2
- Version Eye Movement (King-Devick) x2
- Vision Symptoms Questionnaire (15 questions) x2



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7

Methods




NeuroOptics PLR- Hand-held, easy to use, quick, deployable



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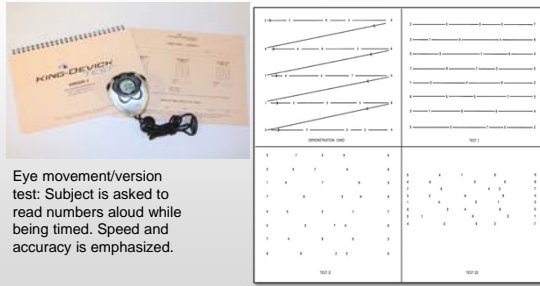
Methods



Near Point Convergence test/Vergence test: checks "eye-teaming" or focusing ability of the two eyes. The tester will use a modified ruler to measure when and if one of the eyes deviates out.

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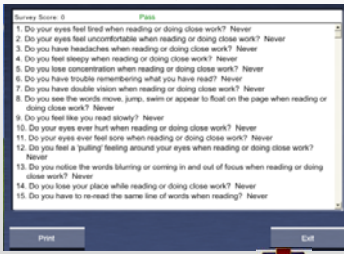
Methods



Eye movement/version test: Subject is asked to read numbers aloud while being timed. Speed and accuracy is emphasized.

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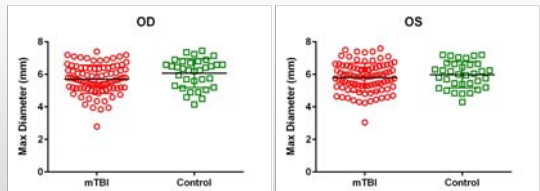
Convergence Insufficiency Symptoms Survey (CISS)



- Score:
 - always (4)
 - frequently (3)
 - sometimes (2)
 - rarely (1)
 - never (0)
- Passing Score ≤ 20

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Maximum Diameter

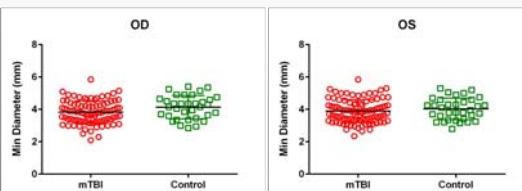


OD: $P = 0.251$

OS: $P = 0.318$

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Minimum Diameter

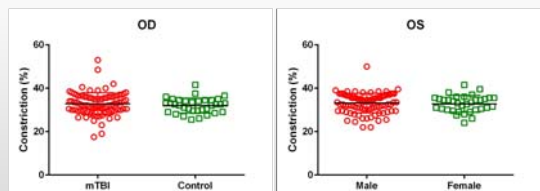


OD: $P = 0.151$

OS: $P = 0.333$

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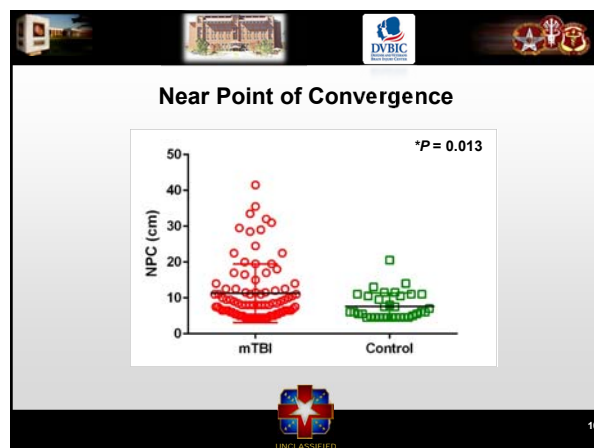
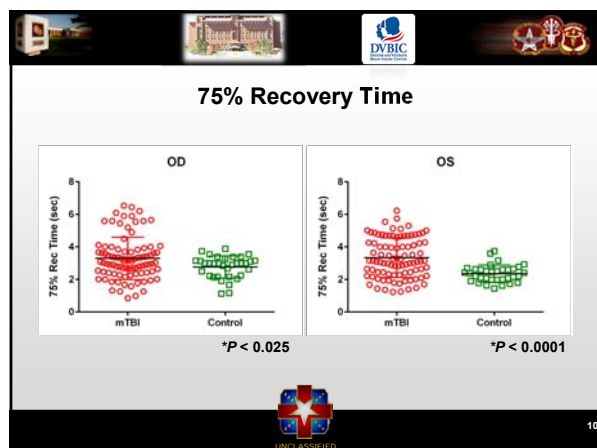
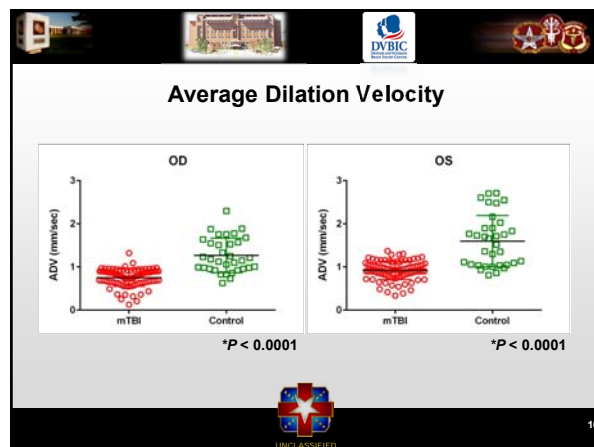
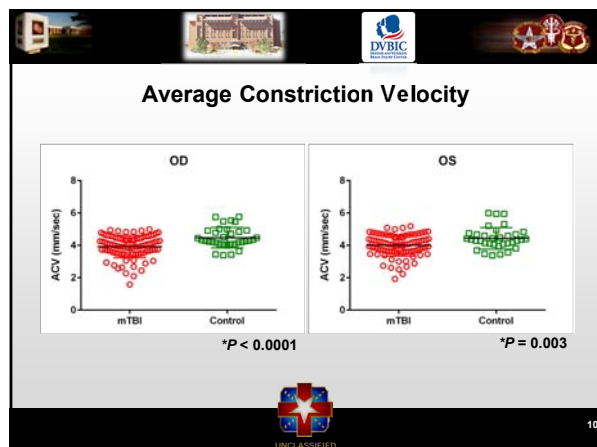
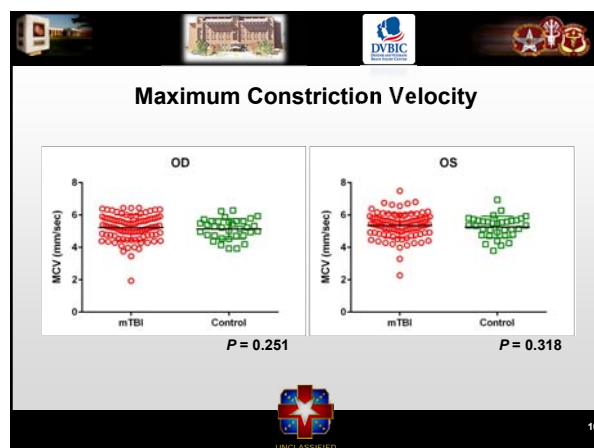
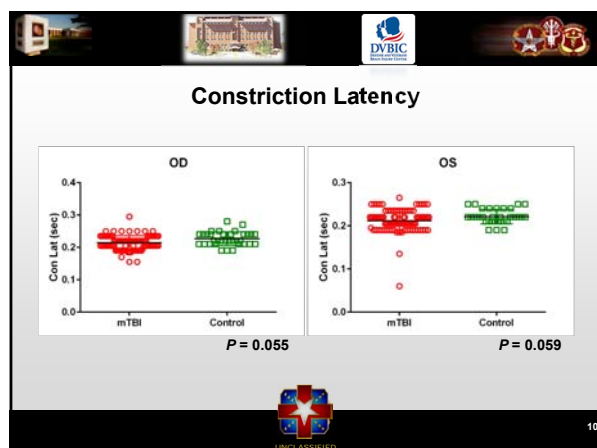
Percent Constriction

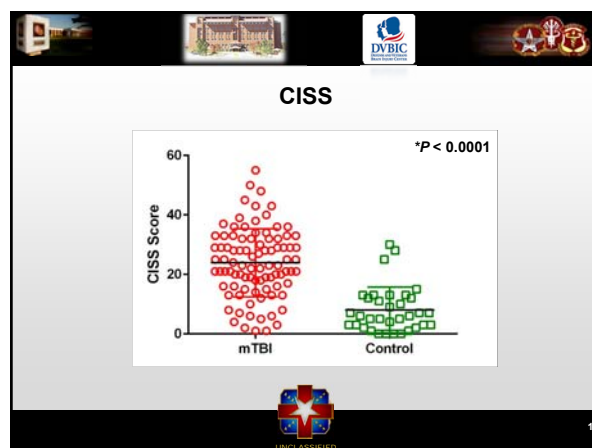
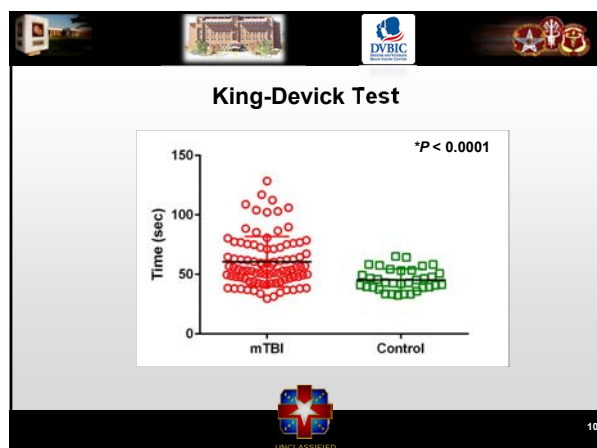


OD: $P = 0.379$

OS: $P = 0.656$

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Discussion

- **Conclusions**
 - Preliminary data for all methods is proving an effective tool.
 - PLR (i.e., ACV, ADV, T75%), NPC, KD test
 - Good correlation with CISS
 - Easily performed by subjects, including mTBI
 - Easily administered by techs and doctors
 - Faster (3 min) than conventional oculomotor examination (20 min)
 - Future Direction
 - Complete data collection for aged-matched control data (non-mTBI group esp. 19-29 yo)
 - Further validation study in theater

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Contribution to Military Medicine

- Provide tool to expedite mTBI diagnosis and management
 - Delegated to technicians/medics
- Strong candidate to determine FFD/RTD status for those Warfighter's with mTBI.

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WAMC Department of Optometry

Questions?



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Validation of Objective Visual System Biomarkers for Early Identification of Warfighters with Acute mTBI/concussion: Preliminary Results

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Optometrist / Department of Optometry / The Geneva Foundation
Womack Army Medical Center, Fort Bragg, NC

Co-Investigators: LTC Jose E. Capó-Aponte; MAJ David V. Walsh
Joseph Y. Dumayas






Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.



The author(s) have no financial interest on any of the products included in this study.

Funded by US Army Medical Research and Materiel Command (USAMRMC), FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP). Award # W81XWH-14-C-0048.

Introduction

- The DOD reported that 333,169 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.4%.
- The diagnosis of mTBI has been a challenge for the military primarily because of the lack of objective assessment tools, overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD), and the interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters.
- Prompt and accurate diagnosis and management of mTBI generally increases an individual's prognosis for neurological recovery and safe return to duty (RTD).
- Premature RTD places Warfighters at greater risk of disability if they suffer an additional concussive trauma. Consequently, there is a quest for objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.


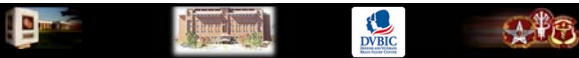
Introduction

Gaps

- Lack of objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.
- Ideal devices are: accurate, quick to perform, non-invasive, causes no discomfort or risk to patient, minimal training, deployable, low cost.
- Valid objective markers are particularly important in the field to assist deployed clinicians to make an accurate determination of fit-for-duty (FFD)/RTD or evacuation.


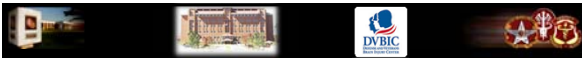
Objectives

- Since approximately 30 areas of the brain, and 7 of the 12 cranial nerves deal with vision, it is not unexpected that the patient with TBI may manifest a host of visual problems, such as pupillary deficit, visual processing delays, and impaired oculomotor tracking and related oculomotor-based reading dysfunctions.
- This study investigates pupillometry, version (i.e., saccades) and vergence (i.e., convergence) eye movements as potential objective biomarkers for acute mTBI.
- We have included 3 eye procedures and 1 questionnaire in this study (10 min).


Methods

- Case-Control Correlational Design
- Approved for 200 AD military personnel aged matched
 - Preliminary data 125 subjects
 - 91 mTBI; age 19-44
 - Medically documented mTBI/concussion during the acute phase, ≤ 3 days
 - ≤ 30 min Loss of Consciousness
 - ≤ 24 hrs Post-Traumatic Amnesia
 - ≤ 24 hrs Alteration of Mental State
 - Glasgow Coma Scale score (13 – 15)
 - Normal structural brain imaging
 - 34 Non-TBI; age 29-44





Methods

- Pupillometry (NeuroOptics PLR-200) x2
- Vergence Eye Movement (NPC ruler) x2
- Version Eye Movement (King-Devick) x2
- Convergence Insufficiency Symptom Survey



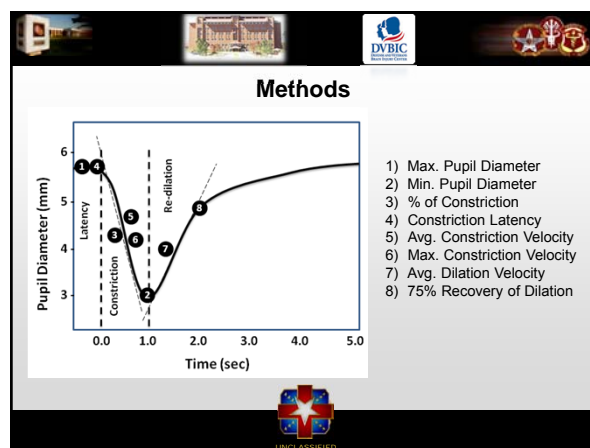
Methods



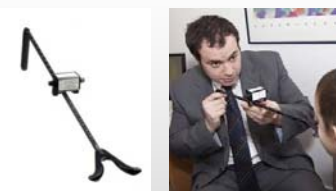
- **Monocular** Infrared pupillometer quantifies PLR under **mesoscopic** conditions ($\sim 3 \text{ cd/m}^2$).
- The subject is asked to fixate with the non-tested eye on a distance target located at **10 feet** away.
- The pupillometer presents a **180 μW light stimulus for 185 ms**.
- It is programmed to **record PLR for 5 seconds**.
- The PLR is **recorded twice** in the right eye and then twice in the left with an interval of about **10 seconds** between the first and second recording.

NeurOptics PLR-200
Hand-held, easy to use, quick, deployable, objective, non-invasive, requires no specialized training and causes no added discomfort or risk to the patient.

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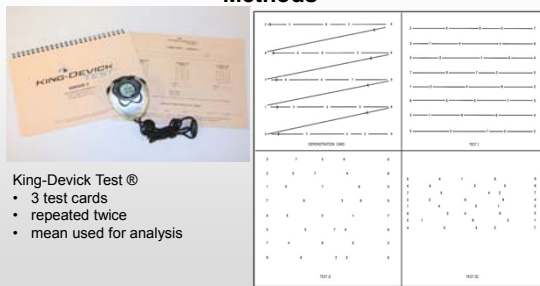
Methods



R.A.F. Near Point Rule (Clement Clarke Ophth.)
20/40 Snellen single letter stimulus.

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Methods




King-Devick Test ©

- 3 test cards
- repeated twice
- mean used for analysis

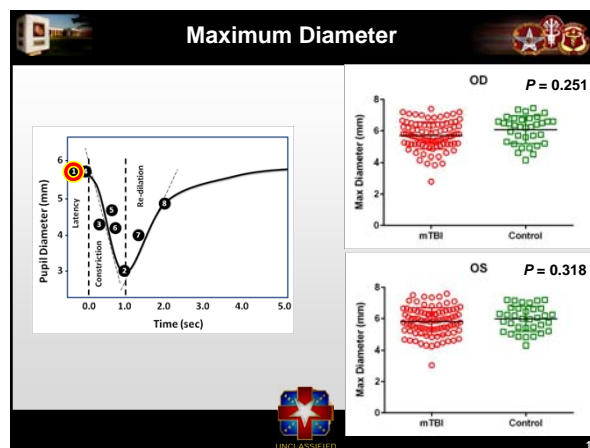
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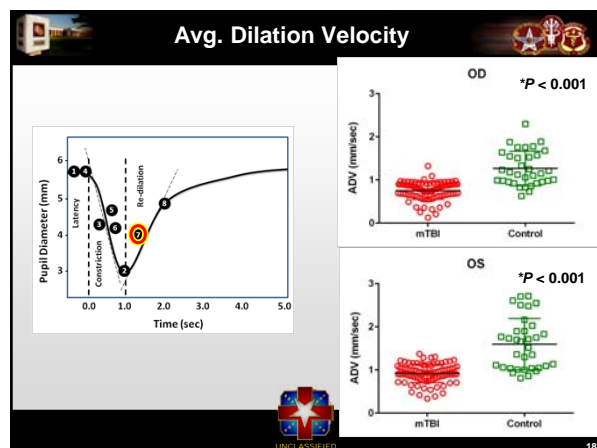
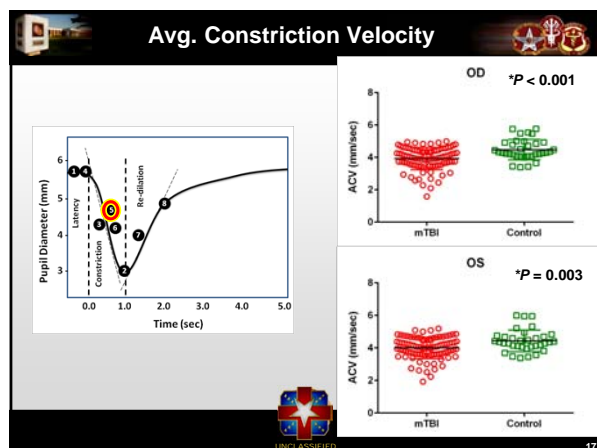
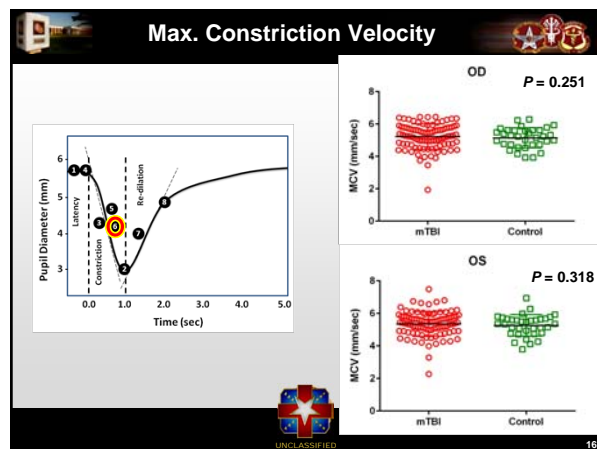
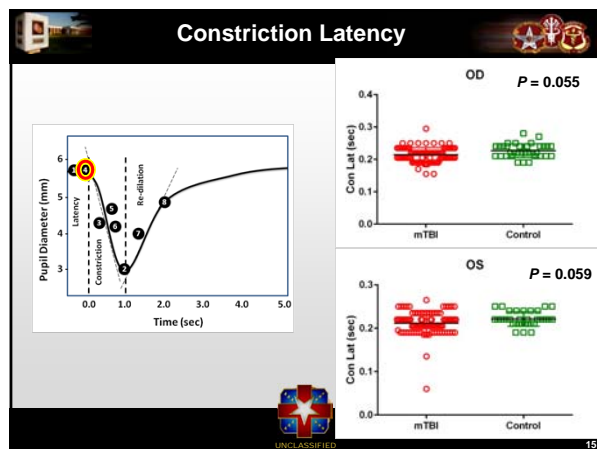
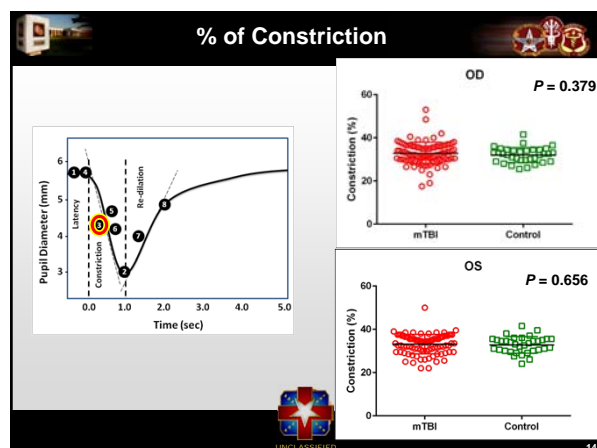
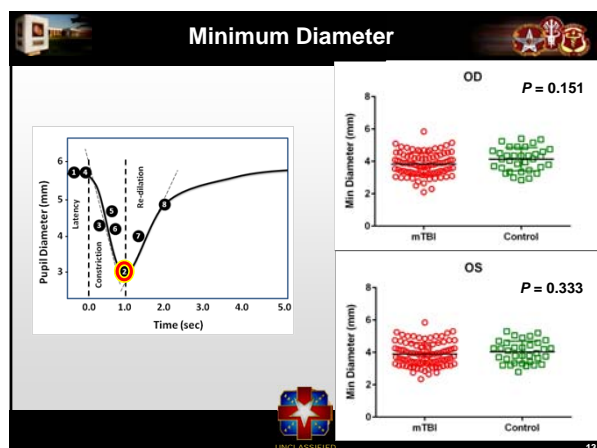
Convergence Insufficiency Symptoms Survey (CISS)

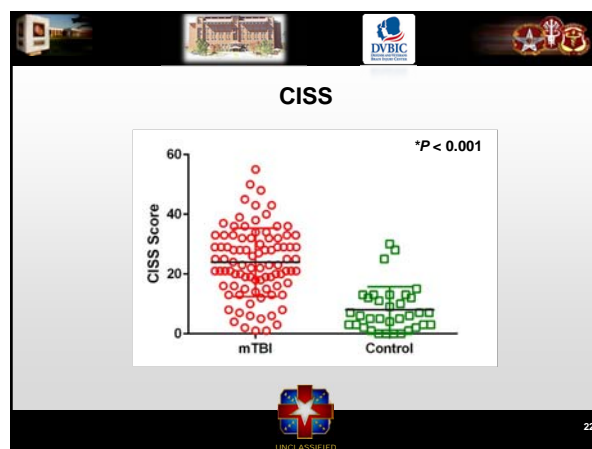
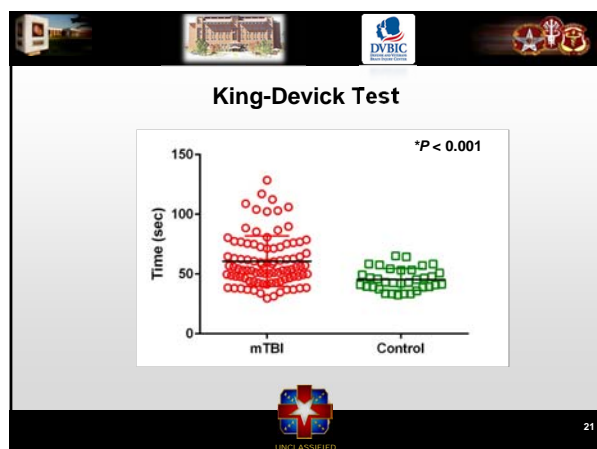
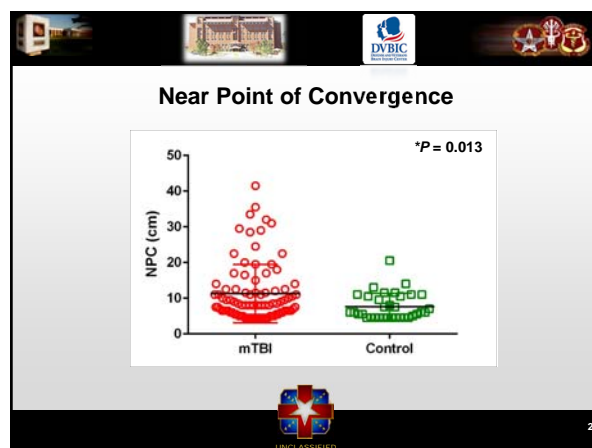
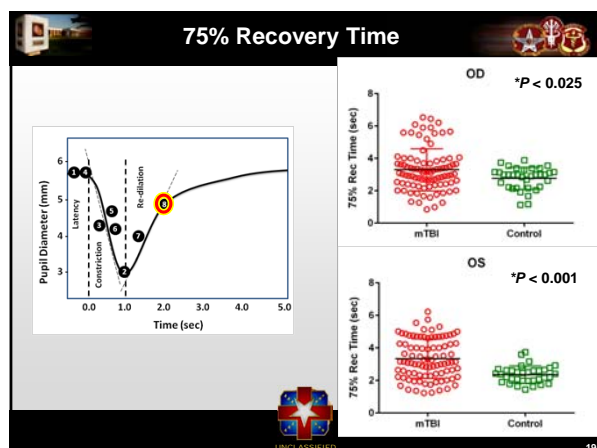


- Score:
 - always (4)
 - frequently (3)
 - sometimes (2)
 - rarely (1)
 - never (0)
- Passing score ≤ 21

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Discussion

- Preliminary data for all methods is proving an effective tool.
 - Objective component: PLR (i.e., ACV, ADV, T75%)
 - Objective and Subjective component: NPC
 - Subjective component: KD test
 - Good correlation with CISS
- Easily performed by subjects, including mTBI
- Easily administered by techs and doctors
- Faster (3 min) than conventional oculomotor examination (20 min)
- Provide tool to expedite mTBI diagnosis and management
- Future Direction
 - Complete data collection for aged-matched control data (non-mTBI group esp. 19-29 yo)
 - This battery of tests could be a strong candidate to determine FFD/RTD status for those Warfighter's with mTBI

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23

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3. Schmidt, K.E. and F.C. Tortella, The diagnosis of traumatic brain injury on the battlefield. Front Neurol, 2012. 3: p. 90.
4. Hoge, C.W., et al., Mild traumatic brain injury in U.S. Soldiers returning from Iraq. N Engl J Med, 2008. 358(5): p. 453-63.
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12. Slobounov, S., et al., Differential rate of recovery in athletes after first and second concussion episodes. Neurosurgery, 2007. 61(2): p. 338-44; discussion 344.
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24



Assessments of the pupillary light reflex (PLR) and eye movements for diagnosis of acute mTBI/concussion in Warfighters

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APPENDIX C

Introduction

The Department of Defense reported that 320,344 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to the third quarter of 2014, with mild TBI (mTBI) accounting for 82.5% of all cases. Unfortunately, Warfighters with TBI are often identified only when moderate or severe head injuries have occurred, leaving more subtle mTBI cases undiagnosed. Currently, there is a lack of mTBI objective biomarkers, and this study aims to identify and validate objective visual biomarkers for mTBI.

Methods

The ongoing study included 91 subjects with acute mTBI (≤ 72 hrs. post injury) and 34 subject controls were evaluated with three tests and a subjective questionnaire. Pupillary Light Reflex (PLR) functions were measured with a handheld monocular infrared pupillometer (NeuroOptics PLR-200) as shown in Fig 1. Saccadic eye movement function was determined with the King-Devick (KD) Test as shown in Fig 2. Near Point of Convergence (NPC) was measured with a near point convergence rule as shown in Fig 3. Finally, the Convergence Insufficiency Symptoms Survey (CISS) was used to assess visual symptoms as shown in Fig 4.

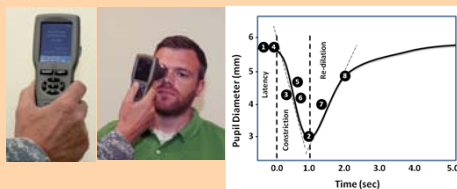


Fig 1. The PLR-200 with demonstration on left; PRL output curve with 8 outcome measures demonstrated on right.



Fig 2. The Near Point Convergence (NPC) ruler on left; demonstration of usage on right.

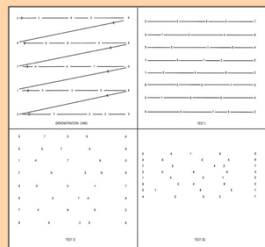


Fig 3. King-Devick (KD) card. From top left to bottom right: Top left: Demo Card; Top right Test 1; Lower left, Test 2; and Lower right, Test 3. Cumulative times are recorded

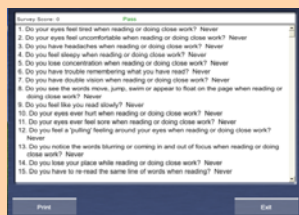


Fig 4. Convergence Insufficiency Symptoms Survey (CISS). Answers/Points for each question are: always (4), frequently (3), sometimes (2), rarely (1), and never (0). A passing score is ≤ 21 .

Results

Of the 8 PLR outcome measures, Average constriction velocity, average dilation velocity and 75% recovery time were significantly reduced in mTBI subjects (Figs 5, 6 and 7)*. In addition, mTBI subjects had significantly higher scores for NPC ($p = 0.0137$), KD Test ($p < 0.0001$), and CISS ($p < 0.0001$), as compared to the controls as shown in Figs 8,9, and 10.

* Update from abstract

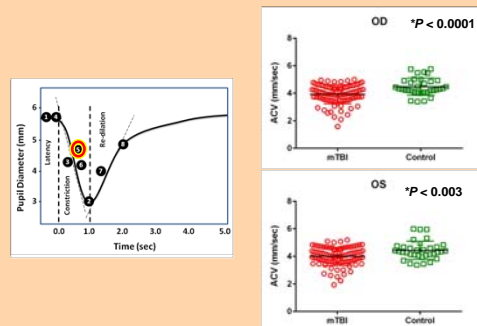


Fig 5. Average Constriction Velocity. Significant differences were seen between mTBI and control groups: OD ($p < 0.0001$); OS ($p < 0.003$).

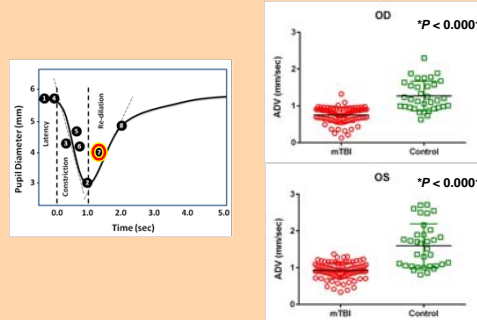


Fig 6. Average Dilation Velocity. Significant differences were seen between mTBI and control groups; OD/OS ($p < 0.0001$).

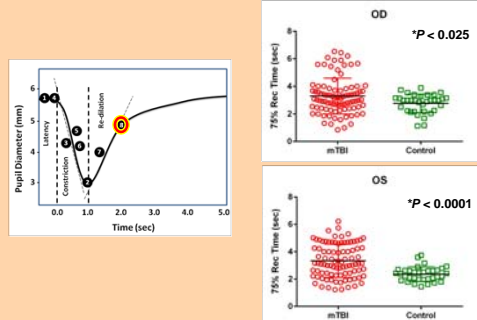


Fig 7. 75% recovery time. Significant differences were seen between mTBI and control groups: OD: ($p < 0.025$); OS: ($p < 0.0001$).

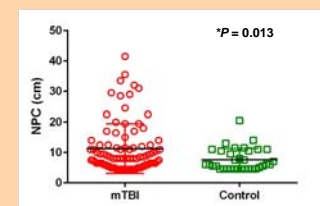


Fig 8. NPC test. Significant differences were seen between mTBI and control groups; OD: $p < 0.013$

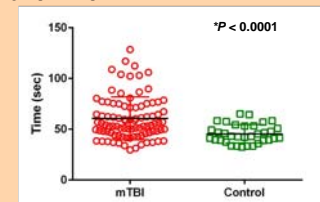


Fig 9. KD test. Significant differences were seen between mTBI and control groups; $p < 0.0001$.

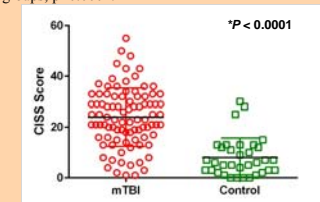



Fig 10. CISS test. Significant differences were seen between mTBI and control groups; $p < 0.0001$.

Results


Determining mTBI biomarker test(s) that can be quickly administered and easily interpreted by frontline providers is vitally important due to the increased risk of sending an injured Warfighter back to the fight and exposing him or her to greater damage to an already injured brain. This is an ongoing study; however, preliminary results presented here strongly suggest the PLR and NPC tests can serve as objective biomarkers for mTBI. The CISS and KD tests also appear to be useful for identifying mTBI, although there is a subjective component to these two tests.




Validation of Visual Objective Biomarkers for Acute non-Blast Mild Traumatic Brain Injury (mTBI)

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Womack Army Medical Center, Fort Bragg, NC



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The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

The authors have no financial interest on any of the products included in this study.

Funded by US Army Medical Research and Materiel Command (USAMRMC), FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP). Award # W81XWH-14-C-0048.




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Introduction

- The DOD reported that over 340,000 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.5%.
- The diagnosis of mTBI has been a challenge for the military primarily because:
 - Lack of objective assessment tools
 - Diagnosis is based on self-reported symptoms by injured Warfighters
 - Overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder
- Prompt and accurate diagnosis and management of mTBI generally increases prognosis for recovery and safe return to duty (RTD).
- Premature RTD places Warfighters at greater risk of disability if they suffer an additional concussive trauma.



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Introduction

Gaps


- Lack of objective markers (e.g., protein, imaging, cognitive, neurosensory) to diagnose Warfighters with mTBI/concussion.
- Valid objective markers are important in the field to assist deployed clinicians to make an accurate determination of fit-for-duty (FFD)/RTD or evacuation.
- DoD WG- Ideal tool must be: accurate, quick to perform, non-invasive, causes no discomfort or risk to patient, minimal training, deployable, and low cost.

Objectives

- This study investigates oculomotor functions as potential biomarkers for acute mTBI: pupillometry, version (i.e., saccades) and vergence (i.e., convergence) eye movements
- Approximately 30 areas of the brain, and 7 of the 12 cranial nerves deal with vision
- It is not surprise that the patient with TBI may manifest visual problems, such as pupillary deficit, visual processing delays, and impaired oculomotor tracking and related oculomotor-based reading dysfunctions.




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Methods: Design



- Case-Control Correlational**
- 200 AD military personnel
 - 100 acute mTBI: 87 males & 13 females
 - Documented mTBI/concussion during the acute phase (≤ 72 hrs)
 - ≤ 30 min Loss of Consciousness
 - ≤ 24 hrs Post-Traumatic Amnesia
 - ≤ 24 hrs Alteration of Mental State
 - Glasgow Coma Scale score (13 – 15)
 - Normal structural brain imaging
 - 100 age-matched Non-TBI; 79 males & 21 females
 - Age ranged from 19 to 44 years; Mean age 26.31 ± 5.81 years



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Methods: Pupillometry

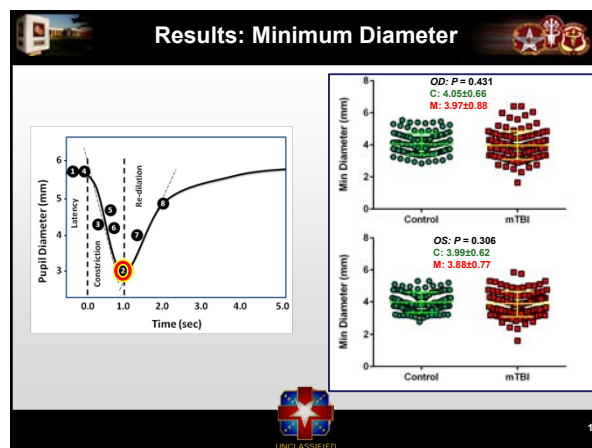
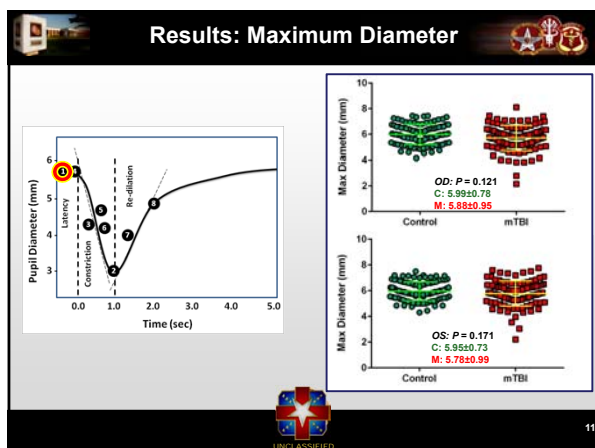
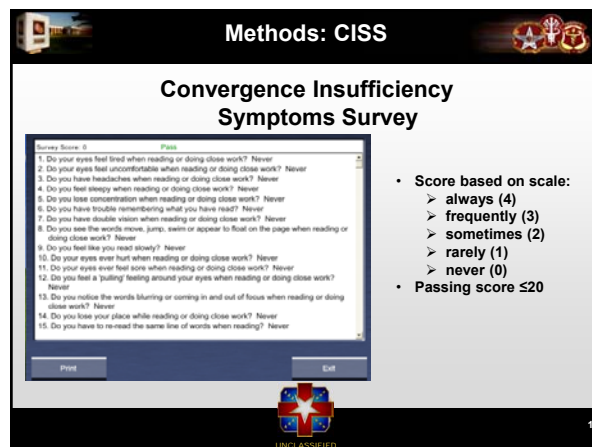
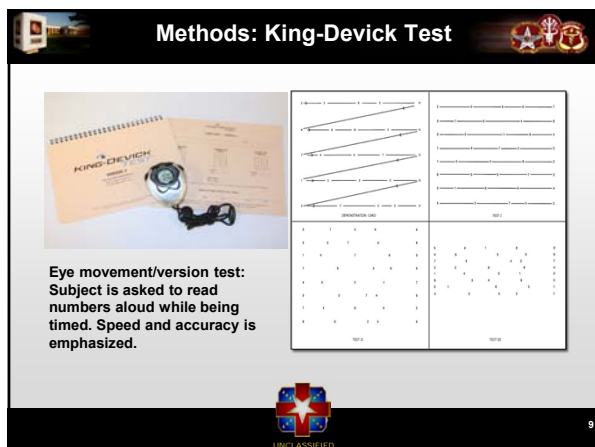
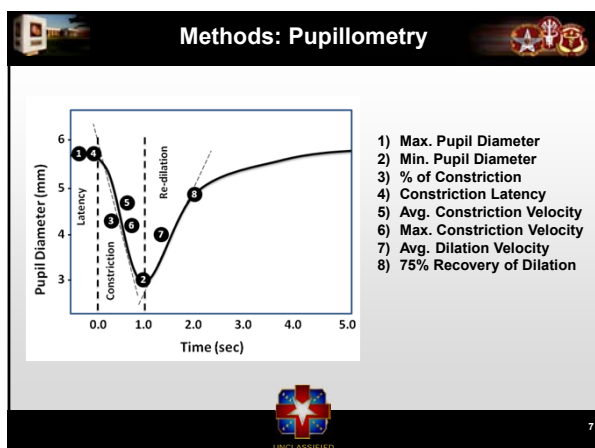
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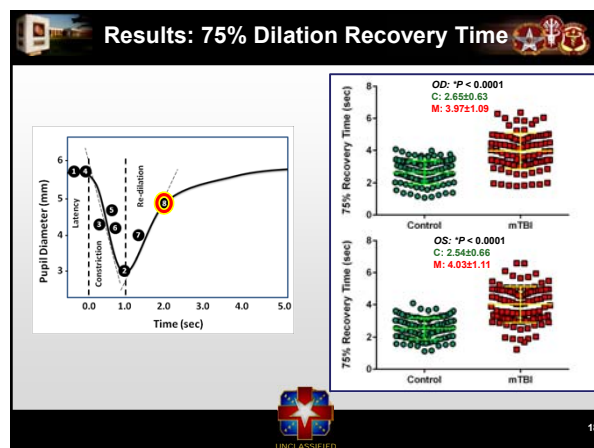
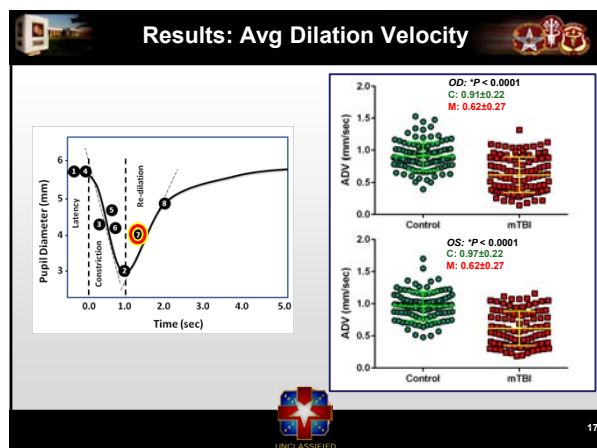
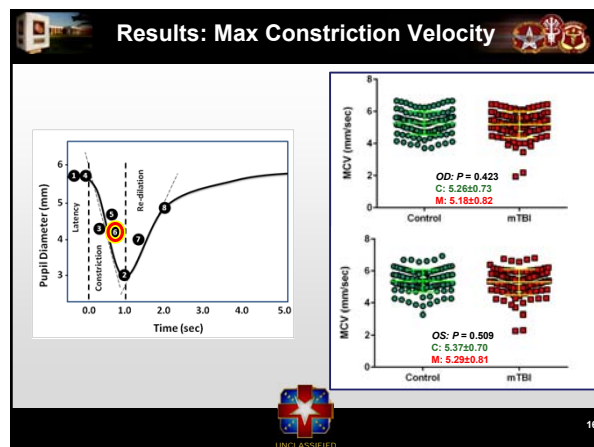
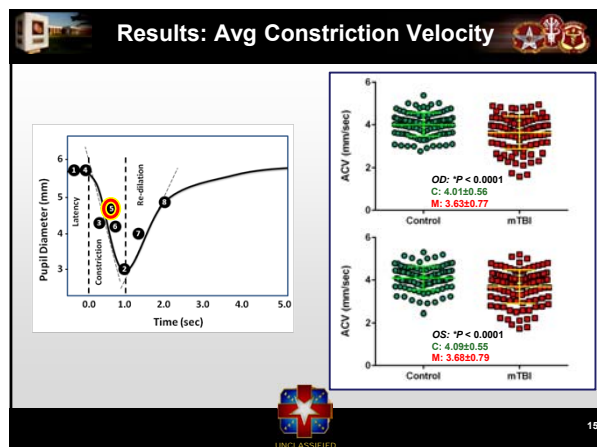
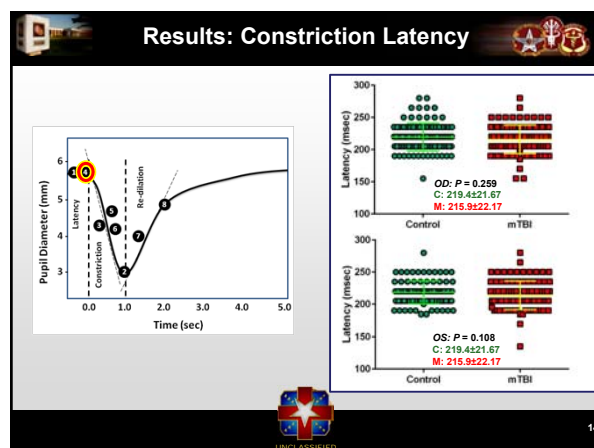
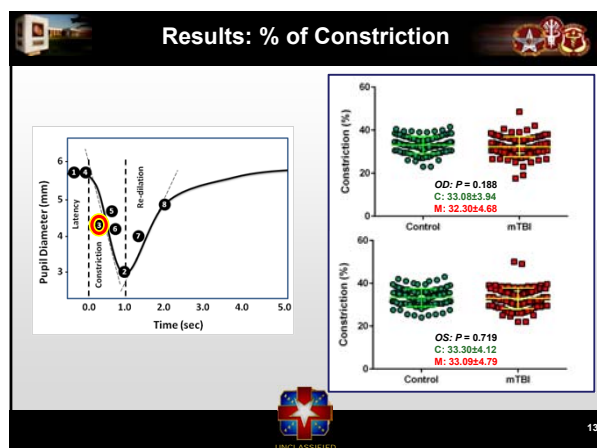
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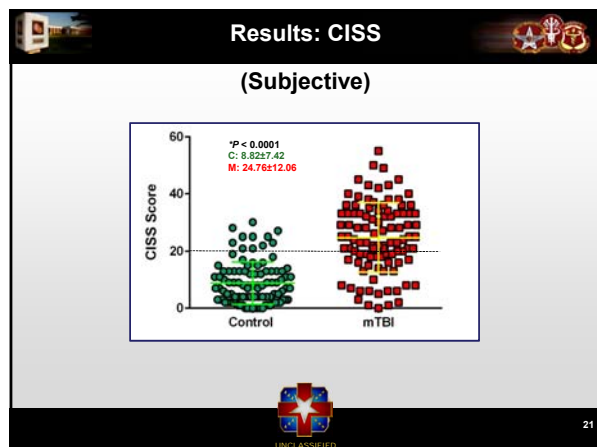
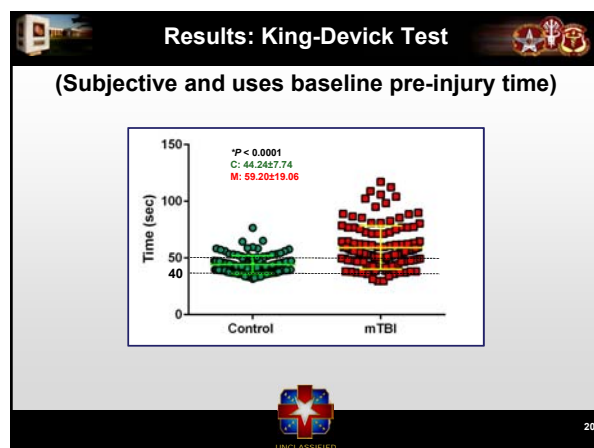
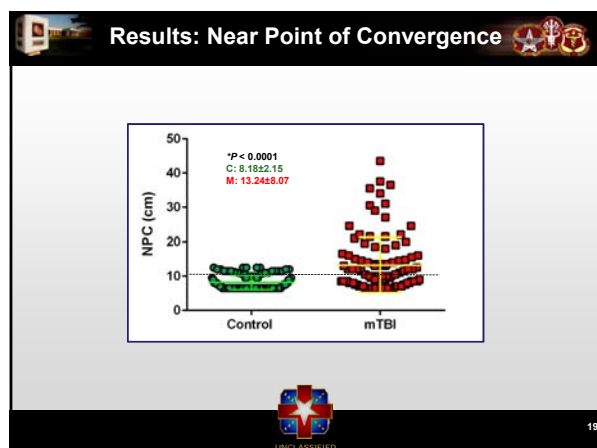
- Monocular Infrared pupillometer under mesoscopic (dim) conditions (~ 3 cd/m²).
- Subject fixated with the non-tested eye on a distance target (10 ft).
- Stimulus: 180 μ W light for 185 msec.
- 8 pupillary light reflex (PLRs) were recorded twice in the right eye and then twice in the left, alternating between eyes with an interval of about 10 seconds between recording.



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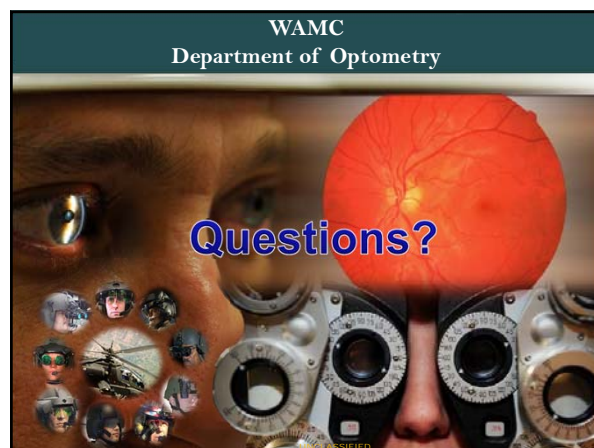







- ### Conclusion
- Oculomotor functions tests are effective tools to identify mTBI
 - Pupillometry: PLR (i.e., ACV, ADV, T75%) – Objective test
 - NPC rule: Convergence eye movement – Objective test
 - KD Test: Saccadic eye movement – Subjective test
 - CISS: visual symptoms has good correlation with affected visual functions
 - Easily performed by subjects, including mTBI
 - Easily administered by technicians (can delegate to medics)
 - Faster (3 min) than conventional oculomotor examination (15 min)
 - Pupillometry = 30 sec; NPC = 15 sec; KD Test = 60 sec; CISS = 60 sec
 - Provide tool to determine RTD (Military Ops) or Return-to-Play (Sport)
 - Future Direction:
 - Develop concussion risk matrix/algorithm based on parameters sensitivity and specificity to assist in RTD/RTP decision
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- ### Acknowledgement
- Womack Army Medical Center (WAMC)
 - Thomas A. Beltran
 - Defense and Veterans Brain Injury Center / WAMC Department of Brain Injury Medicine
 - Dr. Wesley R. Cole
 - The Geneva Foundation / WAMC
 - Joseph Y. Dumayas
 - Dr. Ashley Ballard
 - US Army Aeromedical Laboratory
 - LTC David V. Walsh
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APPENDIX E



Validation Study of Visual Objective Biomarkers for Acute Mild Traumatic Brain Injury

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³Department of Brain Injury Medicine WAMC; Defense and Veterans Brain Injury Center, Fort Bragg, NC



Introduction

The Department of Defense reported that over 340,000 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to 2015, with mild TBI (mTBI) accounting for 82.5% of all cases. Unfortunately, Warfighters with TBI are often identified only when moderate or severe head injuries have occurred, leaving more subtle mTBI cases undiagnosed. Currently, there is a lack of mTBI objective biomarkers, and this study aims to identify and validate objective visual biomarkers for mTBI.

Methods

200 military personnel (100 acute mTBI (≤ 72 hrs) and 100 age-matched Controls; 19 to 44 yrs with mean age 26.31 ± 5.81 yrs) were evaluated with three tests and a subjective questionnaire. Pupillary Light Reflex (PLR) functions were measured with a hand-held monocular infrared pupillometer (NeuroOptics PLR-200 (Fig 1)). Near Point of Convergence (NPC) was measured with a NPC rule (Fig 2). Saccadic eye movement function was assessed with the King-Devick (KD) Test (Fig 3). The Convergence Insufficiency Symptoms Survey (CISS) was used to assess visual symptoms (Fig 4).

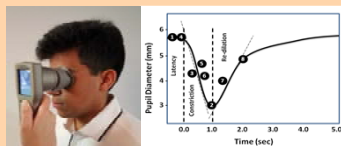


Fig 1. Left: Demonstration of pupil assessment with PLR-200 monocular pupillometer. Right: Typical PRL output curve with eight outcome measures demonstrated: 1) Max. Pupil Diameter; 2) Min. Pupil Diameter; 3) % of Constriction; 4) Constriction Latency; 5) Avg. Constriction Velocity; 6) Max. Constriction Velocity; 7) Avg. Dilation Velocity; 8) 75% Recovery of Dilation.



Fig 2. Left: Near Point Convergence (NPC) rule. Right: demonstration of NPC assessment using a 20/30 Snellen single letter stimulus.



Fig 3. Left: King-Devick (KD) Test. Right: Top left, Demo Card; Top right Test 1; Lower left, Test 2; Lower right, Test 3. Cumulative times were recorded.

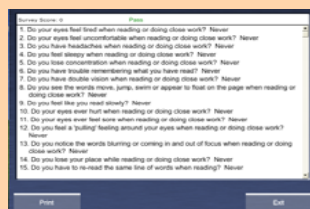


Fig 4. Convergence Insufficiency Symptoms Survey (CISS). Each question was scored based on severity: always (4), frequently (3), sometimes (2), rarely (1), and never (0). A passing score is ≤ 21 .

Results

Of the 8 PLR outcome measures, only average the constriction velocity, average dilation velocity and 75% recovery time were significantly affected in mTBI group (Figs 5, 6 and 7). In addition, mTBI group had significantly higher scores for NPC (receded NPC; $P < 0.0001$), KD Test (took longer; $P < 0.0001$), and CISS (more symptoms; $P < 0.0001$) than Controls as shown in Figs 8, 9, and 10.

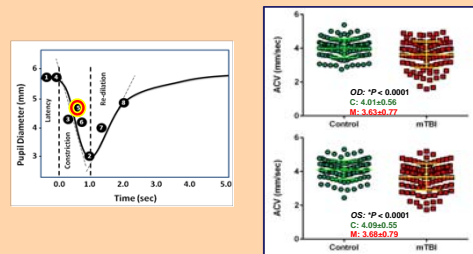


Fig 5. Average Constriction Velocity. mTBI group showed slower average constriction velocity than Control group.

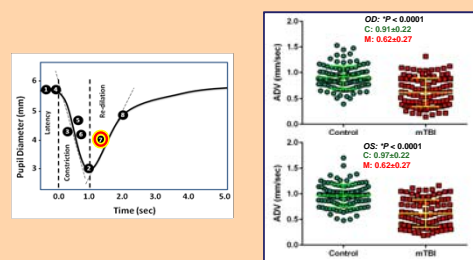


Fig 6. Average Dilation Velocity. mTBI group showed slower average dilation velocity than Control group.

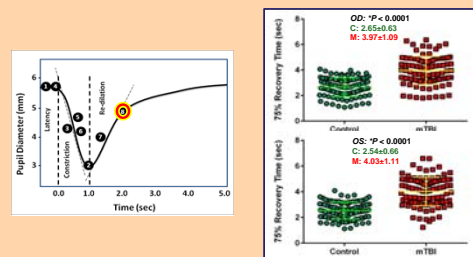


Fig 7. 75% Recovery (re-dilation) Time. mTBI group showed longer time to reach 75% re-dilation than Control group.

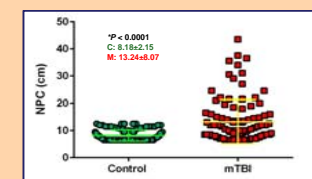


Fig 8. NPC. mTBI group had more receded NPC than Controls.

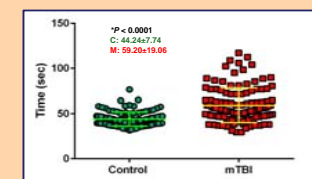


Fig 9. KD test. mTBI group took longer to complete than Controls.

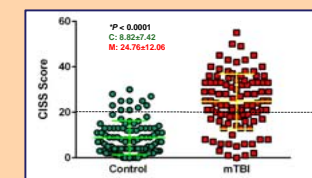



Fig 10. CISS. mTBI group showed more symptoms (higher scores) than Controls.

Conclusion


Results strongly suggest the PLR (i.e., ACV, ADV, T75%) and NPC tests can serve as objective biomarkers for mTBI. The CISS and KD tests also appear to be useful for identifying mTBI, despite of being subjective. These tests that can be quickly administered by non-eye care providers and easily interpreted by frontline providers, which is vitally important due to the increased risk of sending an injured Warfighter back to the fight and exposing him or her to greater damage to an already injured brain.




Validation Study of Visual Objective Biomarkers for Acute Mild Traumatic Brain Injury

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Department of Optometry
Womack Army Medical Center, Fort Bragg, NC



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Disclaimer


The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

The authors have no financial interest on any of the products included in this study.

Funded by US Army Medical Research and Materiel Command (USAMRMC), FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP). Award # W81XWH-14-C-0048.




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Introduction

- The DOD reported that over 340,000 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.5%.
- The diagnosis of mTBI has been a challenge for the military primarily because: lack of objective assessment tools; overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD); interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters.
- Prompt and accurate diagnosis and management of mTBI generally increases an individual's prognosis for neurological recovery and safe return to duty (RTD).
- Premature RTD places Warfighters at greater risk of disability if they suffer an additional concussive trauma.
- Consequently, there is a quest for objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.



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Introduction

Gaps


- Lack of objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.
- Ideal tool must be: accurate, quick to perform, non-invasive, causes no discomfort or risk to patient, minimal training, deployable, and low cost.
- Valid objective markers are particularly important in the field to assist deployed clinicians to make an accurate determination of fit-for-duty (FFD)/RTD or evacuation.

Objectives

- Since approximately 30 areas of the brain, and 7 of the 12 cranial nerves deal with vision, it is not unexpected that the patient with TBI may manifest a host of visual problems, such as pupillary deficit, visual processing delays, and impaired oculomotor tracking and related oculomotor-based reading dysfunctions.
- This study investigates pupillometry, version (i.e., saccades) and vergence (i.e., convergence) eye movements as potential biomarkers for acute mTBI.
- The study included 3 eye procedures and 1 visual symptoms questionnaire
- 10 min test battery.




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Methods: Design


- Case-Control Correlational
- 200 AD military personnel
 - Age ranged from 19 to 44 years; Mean age 26.31±5.81 years
 - 100 acute mTBI: 87 males & 13 females
 - Medically documented mTBI/concussion during the acute phase (≤ 72 hrs)
 - ≤ 30 min Loss of Consciousness
 - ≤ 24 hrs Post-Traumatic Amnesia
 - ≤ 24 hrs Alteration of Mental State
 - Glasgow Coma Scale score (13 – 15)
 - Normal structural brain imaging
 - 100 age-matched Non-TBI; 79 males & 21 females



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Methods: Pupillometry

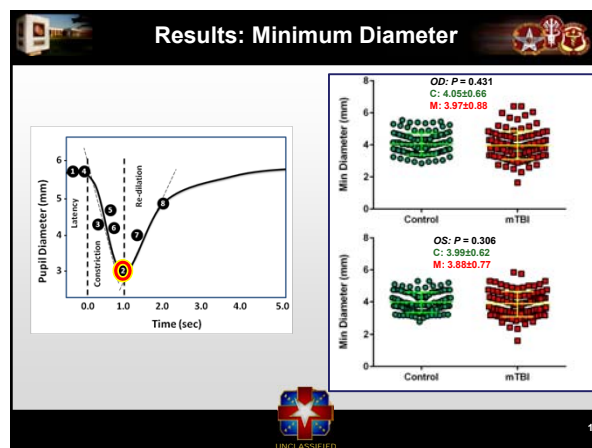
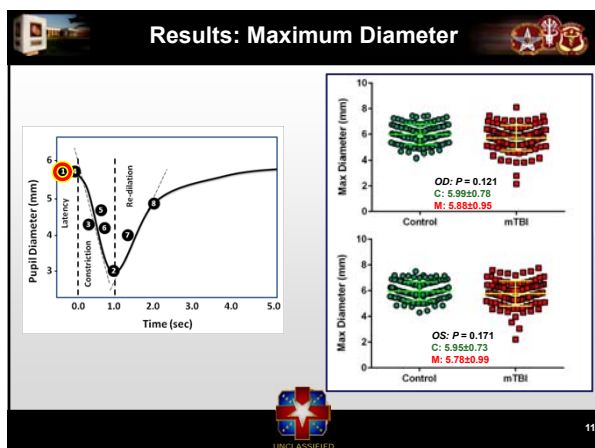
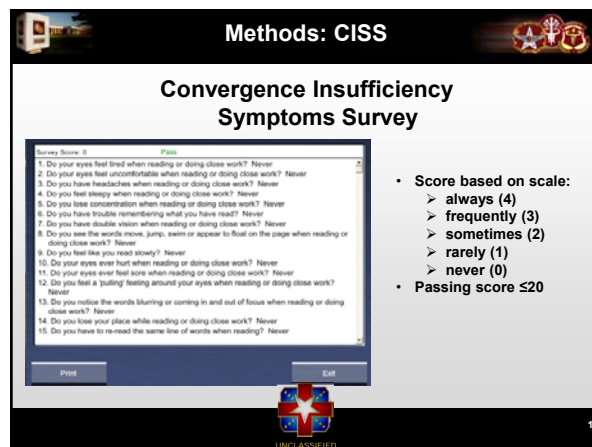
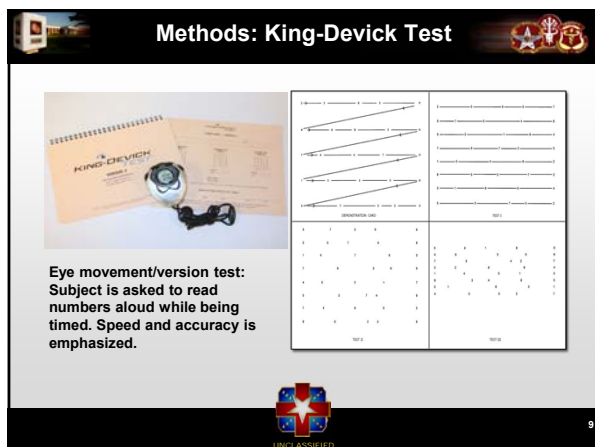
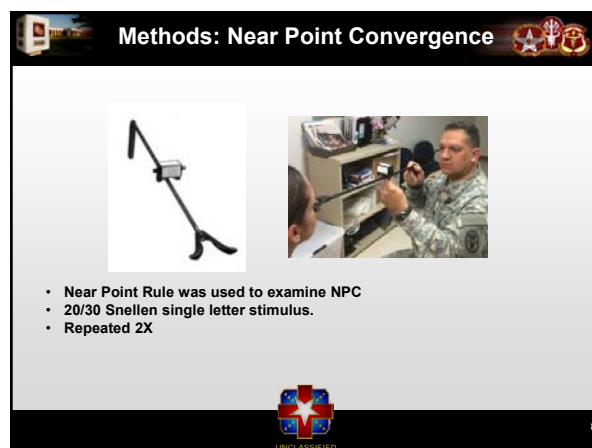
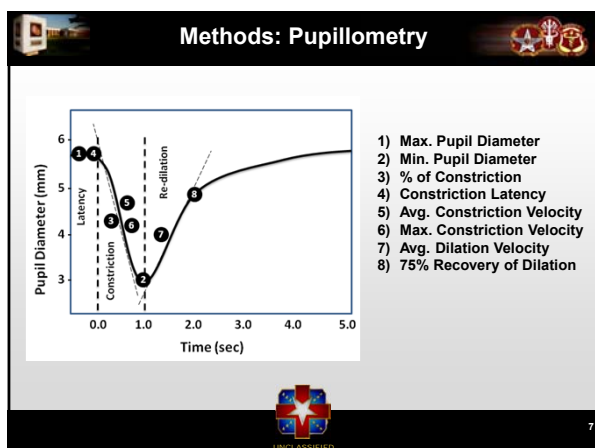


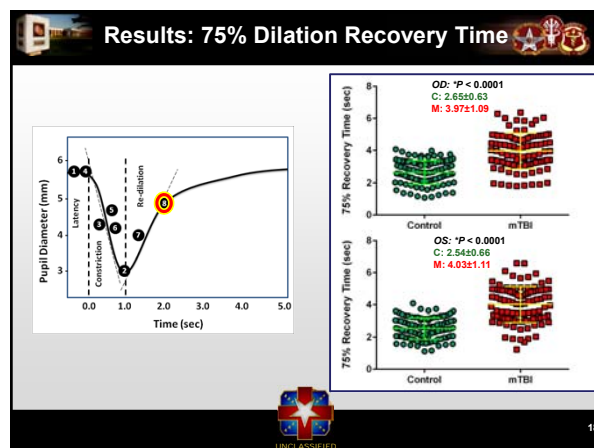
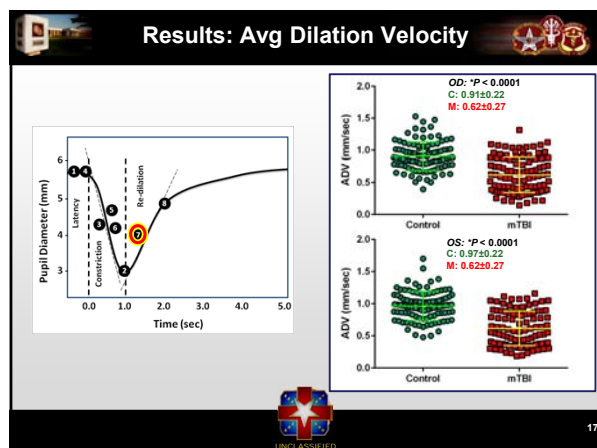
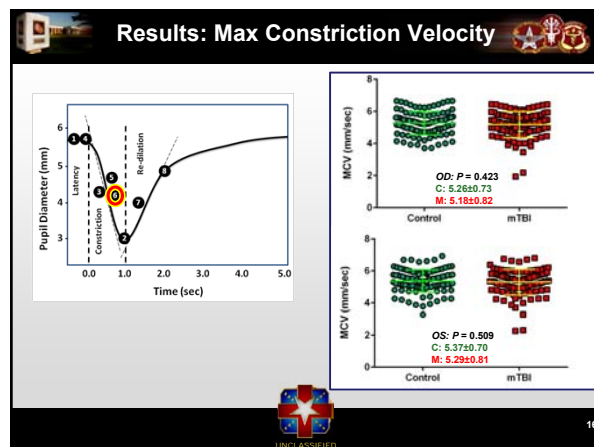
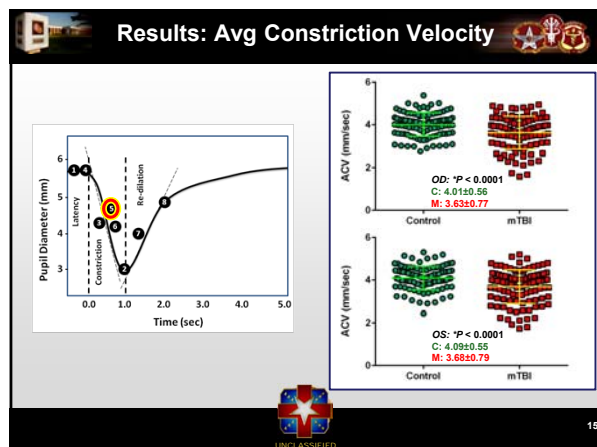
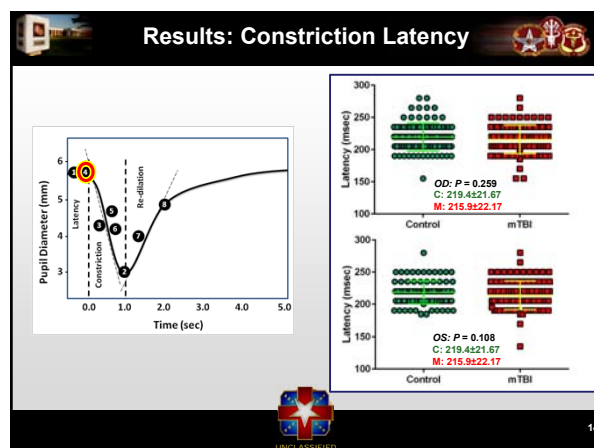
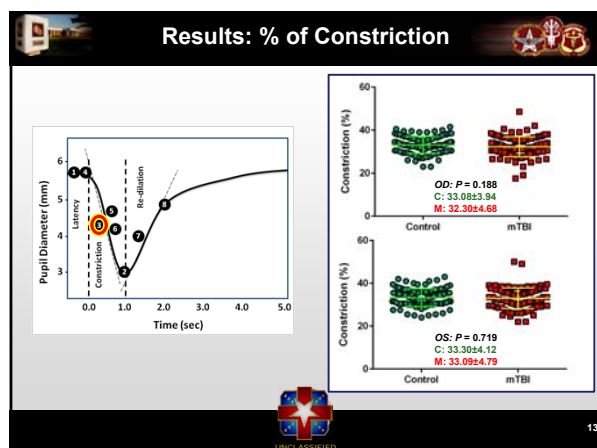
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- Subject fixated with the non-tested eye on a distance target (10 ft).
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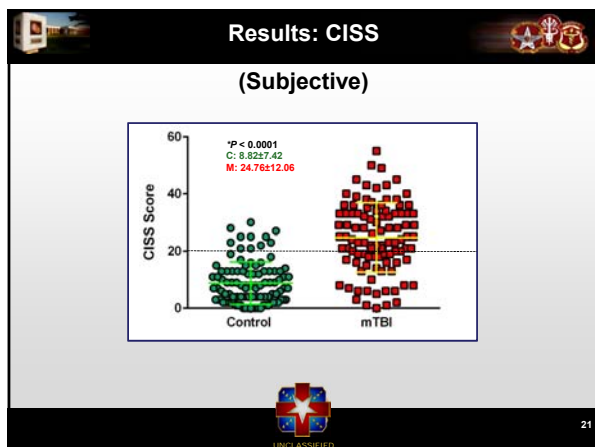
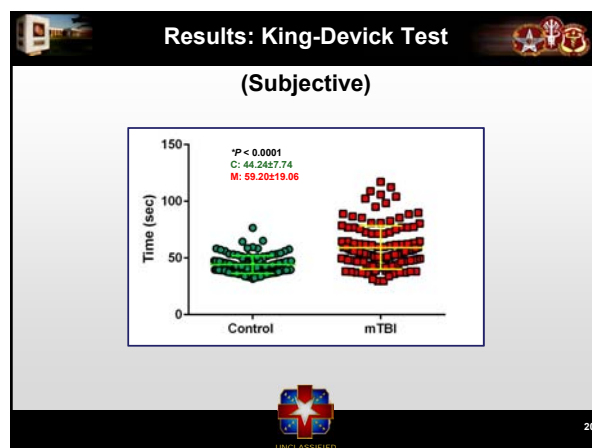
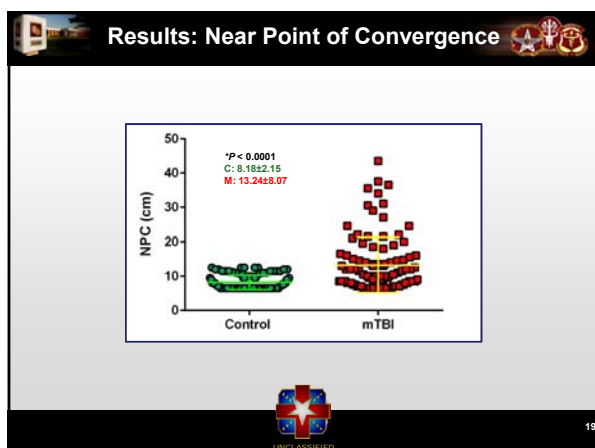
NeuroOptics PLR-200
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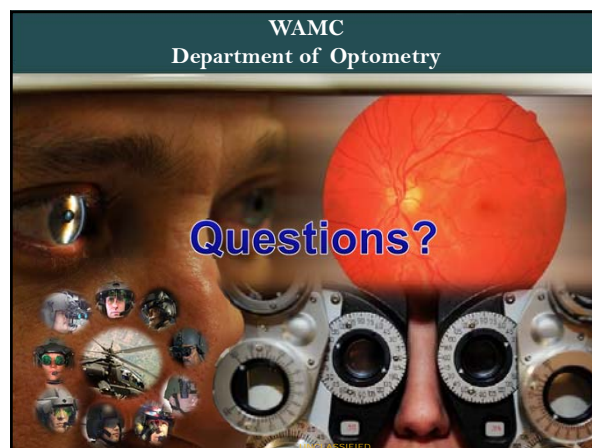







- ### Discussion
- All methods prove effective tool to differentiate mTBI Vs. Controls.
 - Objective component: PLR (i.e., ACV, ADV, T75%)
 - Objective and Subjective component: NPC
 - Subjective component: KD test
 - Good correlation with CISS
 - Easily performed by subjects, including mTBI
 - Easily administered by technicians
 - Faster (3 min) than conventional oculomotor examination (15 min)
 - Provide tool to expedite mTBI diagnosis and management
 - Delegate to technician/medics
 - Future Direction
 - Develop concussion decision matrix/algorithm based on sensitivity and specificity to assist medical personnel make RTD decision
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- ### Acknowledgement
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APPENDIX G Validation of Visual Objective Biomarkers for Acute Concussion

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¹Department of Optometry, WAMC, Fort Bragg, NC; ²Department of Clinical Investigations, WAMC, Fort Bragg, NC; ³U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL; ⁴Geneva Foundation¹Intrepid Spirit, Womack Army Medical Center (WAMC), Defense and Veterans Brain Injury Center, GDIT, Fort Bragg, NC;

Introduction

According to the DoD, 82.5% of the 340,000 diagnosed traumatic brain injuries (TBI) since 2000 have been concussion/ mild TBI (mTBI). Accurate and quick diagnosis of mTBI can assist with return to duty (RTD) decisions. However, there is a lack of objective mTBI biomarkers. As approx. 30 areas of the brain and 7 of 12 cranial nerves deal with vision, it is reasonable to expect visual problems post mTBI. This study aims to identify and validate objective visual biomarkers for mTBI.

Methods

200 military personnel (100 acute mTBI (≤ 72 hrs) and 100 age-matched Controls; 19 to 44 yrs with mean age 26.31 ± 5.81 yrs) were evaluated with three tests and a self-report questionnaire. Pupillary Light Reflex (PLR) functions were measured with a hand-held monocular infrared pupillometer (NeuroOptics PLR-200; **Fig 1**). Near Point of Convergence (NPC) was measured with a NPC rule (**Fig 2**). Saccadic eye movement function was assessed with the King-Devick (KD) Test (**Fig 3**). Visual symptoms were assessed with the Convergence Insufficiency Symptoms Survey (CISS) (**Fig 4**).

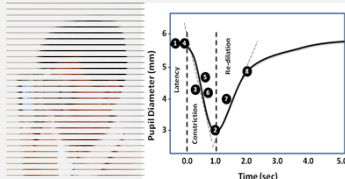


Fig 1. Left: Demonstration of pupil assessment with PLR-200 monocular pupillometer. Right: Typical PRL output curve with eight outcome measures demonstrated: 1) Max. Pupil Diameter; 2) Min. Pupil Diameter; 3) % of Constriction; 4) Constriction Latency; 5) Avg. Constriction Velocity; 6) Max. Constriction Velocity; 7) Avg. Dilation Velocity; 8) 75% Recovery of Dilation.

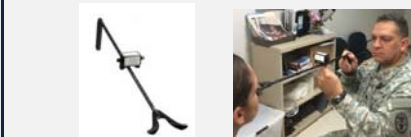


Fig 2. Left: Near Point Convergence (NPC) rule. Right: demonstration of NPC assessment using a 20/30 Snellen single letter stimulus.

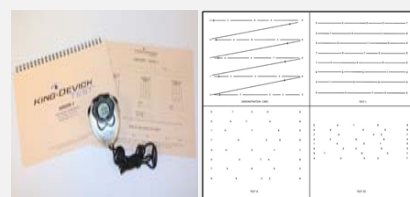


Fig 3. Left: King-Devick (KD) Test. Right: Top left, Demo Card; Top right Test 1; Lower left, Test 2; Lower right, Test 3. Cumulative times were recorded.

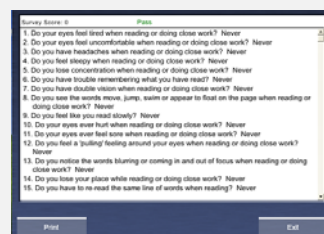


Fig 4. Convergence Insufficiency Symptoms Survey (CISS). Each question was scored based on severity: always (4), frequently (3), sometimes (2), rarely (1), and never (0). A passing score is ≤ 21 .

Results

Three of the eight PLR outcome measures were significantly impacted by group status: Average Constriction Velocity (ACV), Average Dilation Velocity (ADV), and 75% Recovery Time (T75%) (**Figs 5, 6 and 7**). In addition, mTBI group had significantly higher scores for NPC (i.e. receded NPC; $p < 0.0001$), took longer on the KD Test ($p < 0.0001$), and rated more symptoms on the CISS ($p < 0.0001$) than Controls (**Figs 8, 9, and 10**). Effect sizes (Cohen's d) were generally very large.

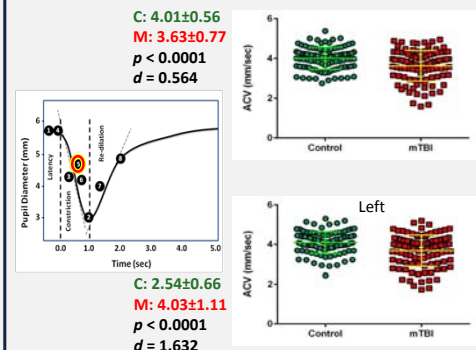


Fig 5. Average Constriction Velocity. The mTBI group showed slower right-sided average constriction velocity than the Control group.

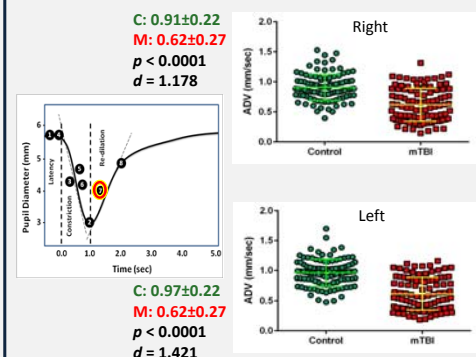


Fig 6. Average Dilation Velocity. The mTBI group showed slower average dilation velocity than the Control group.

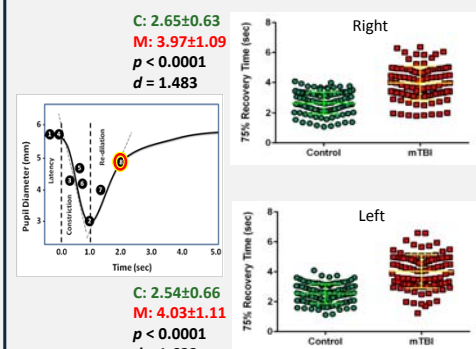


Fig 7. 75% Recovery (re-dilation) Time. The mTBI group showed longer time to reach 75% re-dilation than the Control group.

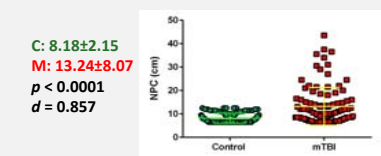


Fig 8. Near Point Convergence. mTBI group had more receded NPC than Controls.

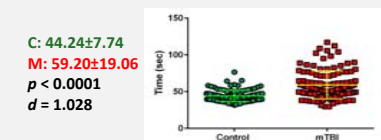


Fig 9. King-Devick Test. mTBI group took longer to complete than Controls.

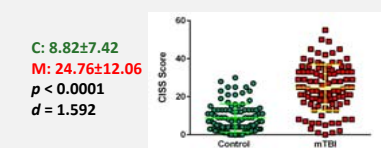


Fig 10. CISS. mTBI group showed more symptoms (higher scores) than Controls.

Conclusion

Results strongly suggest the PLR (i.e., ACV, ADV, T75%) and NPC tests could serve as objective biomarkers for acute mTBI. The CISS and KD tests also appear to be useful for identifying mTBI related problems, despite being more subjective. All of these assessments are deployable, can be quickly administered by non-eye care providers, and are easily interpreted by frontline providers. These factors are important due to the risks associated with prematurely returning an injured Warfighter to duty. Future studies should establish diagnostic algorithms.

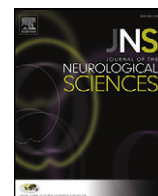
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Funding: US Army Medical Research and Materiel Command, FY13 Department of Defense Medical Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs, Award # W81XWH-14-C-0048.



Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Assessment of the King-Devick® (KD) test for screening acute mTBI/concussion in warfighters



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ARTICLE INFO

Article history:

Received 30 May 2016

Received in revised form 8 September 2016

Accepted 8 September 2016

Available online 11 September 2016

Keywords:

King-Devick (KD) test

Saccades

Mild traumatic brain injury (mTBI)

Military

ABSTRACT

Objectives: The Department of Defense reported that 344,030 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to 2015, with mild TBI (mTBI) accounting for 82.3% of all cases. Unfortunately, warfighters with TBI are often identified only when moderate or severe head injuries have occurred, leaving more subtle mTBI cases undiagnosed. This study aims to identify and validate an eye-movement visual test for screening acute mTBI.

Methods: Two-hundred active duty military personnel were recruited to perform the King-Devick® (KD) test. Subjects were equally divided into two groups: those with diagnosed acute mTBI (≤ 72 h) and age-matched controls. The KD test was administered twice for test-retest reliability, and the outcome measure was total cumulative time to complete each test.

Results: The mTBI group had approximately 36% mean slower performance time with significant differences between the groups ($p < 0.001$) in both tests. There were significant differences between the two KD test administrations in each group, however, a strong correlation was observed between each test administration.

Conclusions: Significant differences in KD test performance were seen between the acute mTBI and control groups. The results suggest the KD test can be utilized for screening acute mTBI. A validated and rapidly administered mTBI screening test with results that are easily interpreted by providers is essential in making return-to-duty decisions in the injured warfighter.

Published by Elsevier B.V.

1. Introduction

The Department of Defense reported that 344,030 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to 2015, with mild TBI (mTBI) accounting for 82.3% of all cases [1]. Warfighters who experienced mild head impacts producing subtler injuries are harder to diagnose versus those warfighters who have suffered moderate to severe head injuries. Some of the confounders in identifying post-concussive problems include the overlap of symptoms in co-morbid disorders such as post-traumatic stress disorder (PTSD) [8,20], and the difficulty in diagnosing self-reported symptoms to the health provider [19].

A recently convened military mTBI diagnostics workshop emphasized the lack of biomarkers or diagnostic tests for mTBI [15,19]. Consequently, there is a quest for objective markers (e.g., protein, imaging, cognitive, neurosensory) to diagnose warfighters with mTBI/concussion [15]. In combat or training scenarios, warfighters having cognitive and neurosensory difficulties triggered by an mTBI event can put lives and

safety in danger when operating in environments that depend on optimal situational awareness and perception of the surrounding environment. Having a rapid and accurate diagnostic tool in the management and treatment of mTBI generally improves an individual's prognosis for neurological recovery [10,17,18] and safe return-to-duty (RTD) [9,11,25]. Valid diagnostic tests are particularly important in theater to assist deployed clinicians in making accurate determination of RTD or evacuation from theater. Returning a warfighter with a possible head injury back to duty prior to recovery puts the warfighter at a greater risk of disability if they suffer further brain trauma [22].

Seven of the twelve cranial nerves, along with approximately 30% of the brain [23,24], are involved in visual processing; therefore, it should be no surprise that oculomotor/saccadic eye movements are commonly affected in individuals with mTBI/concussion [2–4,7]. Saccades are rapid movements of the eyes as they shift fixation from one point to another. The King-Devick® (KD) test is a rapid, easy-to-administer eye movement test developed in 1976, and used to assess dyslexia and other learning disabilities [5]. In recent studies, the KD test has been examined as a potential screening tool for assessment of concussions in sports such as boxing, football, hockey, soccer, and rugby [5,6,12,13]. All of

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these studies have demonstrated promising results in assessing pre- and post-concussive differences which suggests the KD test could potentially be used to identify warfighters who have suffered mTBI/concussion. Finally, test-retest reliability for the KD test has been examined in previous studies and shown to be high, with intraclass correlations of 0.97 (95% confidence interval [CI] 0.90, 1.0) between measurements in the absence of concussion [5,6].

The purpose of this study was to assess an “off-the-shelf” eye movement test, the King-Devick®, in those who have experienced an acute mTBI/concussion. The results of this study may validate the use of an easy-to-administer and interpret eye movement test as a post-mTBI screening tool which can be added to a range of concussion assessment tools in assisting health-care providers with RTD decisions in warfighters.

2. Methods

2.1. Subjects

Two-hundred active duty military personnel were recruited for the study. The subjects were divided into two groups: those with diagnosed acute mTBI (≤ 72 h; $n = 100$) and age-matched controls ($n = 100$). The diagnosis of mTBI was made by primary care providers at a military Concussion Care Clinic based on a Glasgow Coma Scale score from 13 to 15, normal structural brain imaging, if available, and meeting at least one of the following criteria: any alteration of mental state; loss of consciousness though not exceeding 30 min; posttraumatic amnesia of no more than 24 h. Inclusion criteria for the control group were any active-duty service member with no history of mTBI/concussion. The study was approved by the Womack Army Medical Center Institutional Review Board and the US Army Medical Research and Materiel Command (USAMRMC), Human Research Protection Office. Each subject

was provided written informed consent before participating in the study.

2.2. Equipment & procedures

The KD test used to evaluate saccadic eye-movement performance is shown in Fig. 1. The KD test is based on the measurement of the speed of rapid number naming and involves reading aloud a series of single-digit numbers from left to right on three progressively more difficult test cards. Standardized instructions provided with the instrument were used. The KD test was administered in a well-lit room at a normal reading distance (i.e., 40 cm) with the subject's best near-visual correction, if needed (e.g., glasses, contact lenses). To begin, a demonstration card was shown to the subject with explicit instructions on how to perform the test. The subject was instructed to read the numbers as fast as possible without making errors. If error(s) were made, and the subject returned to correct the error(s), then the error(s) were not counted. The subjects were instructed not to use their hands or fingers on the card to assist during the testing. Speed and accuracy were emphasized throughout the test and the cumulative times were recorded by the tester. The cumulative time was measured with a stopwatch, and the test was administered twice with an approximately 5-minute gap between each test administration.

2.3. Statistical analyses

Means and standard deviations were calculated for each group with cumulative time to complete each KD test being the outcome measure. A Shapiro-Wilk test for normality was performed on all data, and indicated the presence of non-normal distributions. Thus, in each group, a Wilcoxon Matched-Pairs Signed-Rank Test was used to confirm test-retest reliability by comparing the KD test results from time 1 to time 2. A Mann-Whitney U was performed to compare control vs. mTBI group

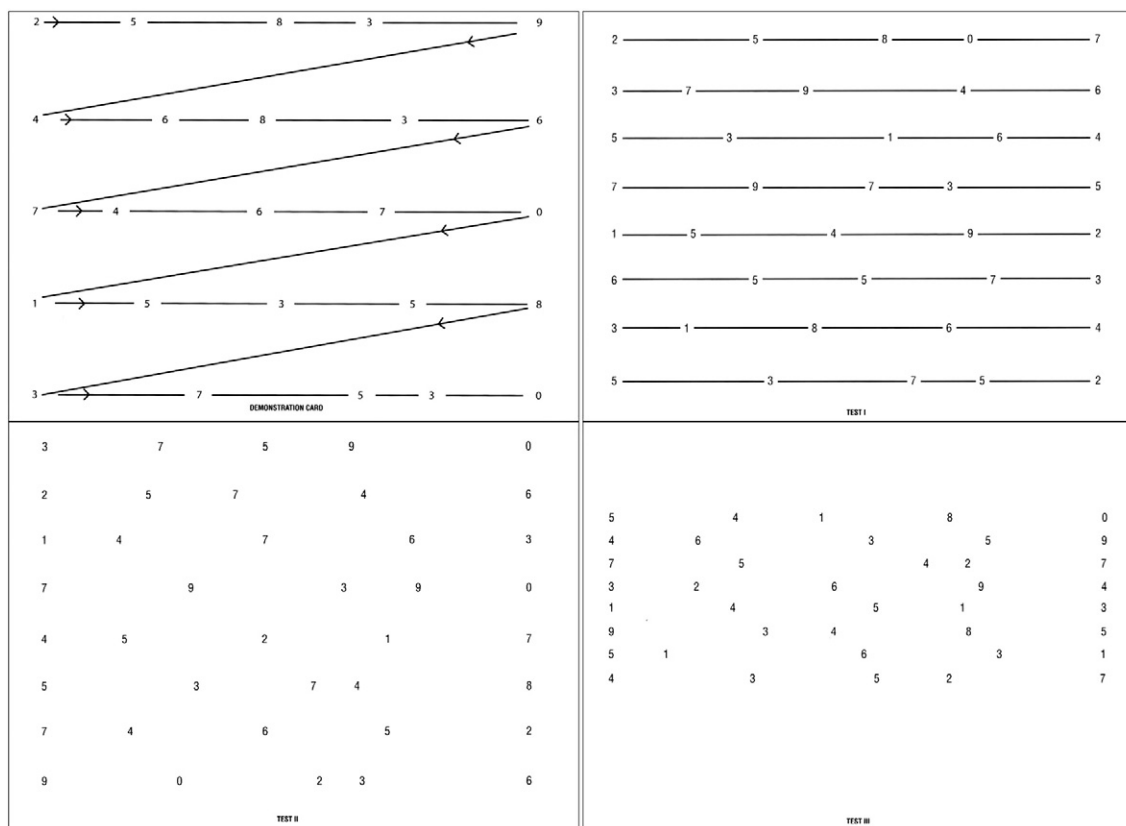


Fig. 1. King-Devick cards. The first card (top left) is the demonstration card, and subsequent cards are tests I, II, and III.

performance. Since non-parametric statistical analyses were performed on the groups' data, medians (Mdn) and Interquartile Ranges (IQR) were also reported. Statistical significance was set at $p < 0.05$, and statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 20.0 software and GraphPad Prism 6 (GraphPad Software, San Diego, CA).

3. Results

3.1. Demographics & mechanisms of injury

Demographics information of both groups is shown in Table 1. The mean age of both groups was 26.31 ± 5.83 . In both groups, subjects were predominantly male (87% mTBI vs. 79% controls), Caucasian, and most were junior enlisted (E1–E4) Army soldiers. The mechanisms of injury (MOI) of the acute mTBI group are shown in Table 2. Out of the 100 mTBI subjects, a little more than two-thirds were injured due to parachute jump. Each of the remaining MOI reported (blunt force, combatives, fall, motor vehicle accident, sports/recreational activities, other) accounted for <10% of the injuries in this sample population. None of the subjects suffered from a blast-induced mTBI.

3.2. King-Devick test

Descriptive statistics are shown in Table 3. In test 1, the mean cumulative test times for the mTBI and control groups were 62.01 ± 19.91 s (95% CI [58.06, 65.96]) and 45.65 ± 8.31 s (95% CI [44.00, 47.30]), respectively. In test 2, the mean cumulative test time for the mTBI and control groups were 58.57 ± 19.71 s (95% CI [54.64, 62.47]) and 43.40 ± 8.10 s (95% CI [41.80, 45.01]), respectively. The Wilcoxon Matched-Pairs Signed-Rank Test revealed a significance difference between the two test administrations (time 1 versus time 2) in both groups (controls: $z = -5.90$, $p < 0.001$; mTBI: $z = -5.32$, $p < 0.001$). Due to the significant differences between the two tests administered to both study groups, a correlation analysis was performed. Spearman's ρ 's were 0.918 ($p < 0.001$) and 0.949 ($p < 0.001$) for repeated tests for the control and mTBI groups, respectively (Fig. 2).

For test time 1, a Mann-Whitney U test revealed significant differences between the mTBI (Mdn = 58.29, IQR = 49.41–72.97 s) and control (Mdn = 44.93, IQR = 39.21–50.49 s) groups, $U = 2168$, $p \leq 0.001$ (Fig. 3). Similarly, in time 2, a significant difference was found between the mTBI (Mdn = 53.49, IQR = 45.70–70.94 s) and control (Mdn =

Table 2

Mechanisms of injury.

	Percent (%)
Blunt force	5
Combative training	2
Fall	7
Parachute jump	69
Motor vehicle accident	6
Sports/recreational activities	5
Other	6

42.80, IQR = 37.13–47.97) groups, $U = 2380$, $p \leq 0.001$ (Fig. 3). Finally, the mTBI mean cumulative reading times were approximately 36% slower in both administration times 1 and 2.

4. Discussion

The primary aim of the present study was to investigate the potential use of the KD test, an eye-movement screening test, as a diagnostic tool for warfighters who may have suffered an mTBI/concussion event. Results from the study demonstrated significant differences in KD test performance between the acute mTBI and age-matched control groups. The KD test showed a little more than one-third slower reading time in the mTBI group. For both groups, there was a statistically significant difference between the two test administration times, though the test-retest correlations were strong, indicating solid test-retest reliability in both the mTBI and control groups.

Numerous previous studies have validated the KD test on athletes, though with study subjects receiving baseline assessments and serving as their own controls [5,6,12,13]. Prior KD test studies utilizing separate control groups have shown significant differences between the controls and experimental groups; however, their experimental groups consisted of patients with Parkinson's disease [14] and multiple sclerosis [16], not acute mTBI as seen in the present study. But a recent KD test study on subjects recruited from an emergency department did include acute (within 72 h) mTBI patients and controls [21]. Their study did not find significant differences in KD test performance between the mTBI and control groups. This finding was contrary to previous sports-related concussions studies, and Silverberg et al. primary argument concerning the different results was their patients' mean assessment time was 31 h post-injury, whereas, the data collected in the other sports-related injury studies referenced here was within 60 min post-injury. Silverberg et al. theorized "sensitivity of the K-D may dissipate rapidly over the hours to days following an mTBI." In the present study, the subjects' mean assessment time was 2.02 days post-injury; therefore, the average post-injury was more comparable to the Silverberg et al. study. The differences in results between the studies could be due to the approximately 3.4 times greater sample size in the present study (200 vs. 59).

A limitation of the present study was no baseline KD testing was performed on the two groups of subjects. The KD test decision matrix in screening head injuries is based upon differences in baseline and post-injury KD times of the injured individuals. However, the study's significant result between the groups does strongly suggest that

Table 1
Demographics.

	mTBI (n = 100)	Controls (n = 100)
Age (years \pm SD)	26.31 \pm 5.83	26.31 \pm 5.83
Sex (%)		
Males	87	79
Females	13	21
Branch		
Army	99	97
Marines	1	0
Navy	0	1
Air force	0	2
Military rank (%)		
E1–E4	62	54
E5–E6	25	17
E7–E9	3	2
CW2–CW3	2	2
O1–O5	8	25
Ethnicity (%)		
Caucasian	60	58
African-American	14	18
American-Indian	3	1
Hispanic	14	13
Asian	3	6
Other	6	4

SD = standard deviation.

Table 3
Descriptive statistics.

	mTBI		Controls	
	Mean \pm SD	Median (IQR)	Mean \pm SD	Median (IQR)
Test 1	62.01 \pm	58.29	45.65 \pm	44.93
(s)	19.91	(49.41–72.97)	8.31	(39.21–50.49)
Test 2	58.57 \pm	53.49	43.40 \pm	42.80
(s)	19.71	(45.70–70.94)	8.10	(37.13–47.97)

s = seconds; SD = standard deviation; IQR = Interquartile Range.

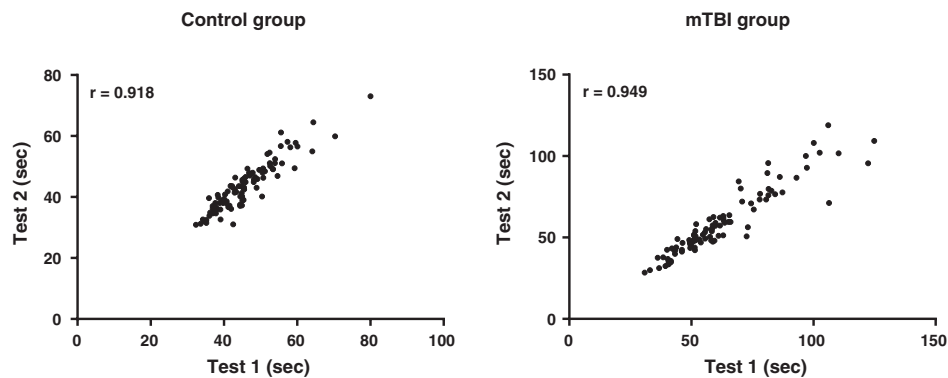


Fig. 2. Correlation graphs of KD test-retest reliability in control (left) and mTBI (right) groups. Spearman's ρ 's were 0.918 ($p < 0.001$) and 0.949 ($p < 0.001$) for repeated tests for the control and mTBI groups, respectively.

baseline testing should be performed on warfighters prior to exposure to combat or training environments.

Finally, there are two drawbacks to the KD card test. First, a confounding variable with test results is the reading speed is controlled by the subject. This confounder may produce false positive or false negative results in soldiers. To reduce this issue, the KD test should not be used as a stand-alone screening test for mTBI events. Other screening tests, preferably objective, should be used in combination with the KD test when determining RTD. Second, the KD card test is that it does not provide information on what the eyes or visual system are doing while performing the test. To address this limitation, KD test technology has advanced with automated testing, and an automated KD test with eye tracking integrated is currently undergoing test-retest validity at US Army Aeromedical Research Laboratory in a separate study. However, a disadvantage of such an automated test is that it has a larger physical "footprint" (compared to KD test card), and thus may have difficulties being used as a screening device in deployment settings. The ideal screening device would be developed into smaller device such as a smartphone or tablet. With ever-advancing technology at the fingertips of front-line providers, having a quick mTBI assessment tool can not only help make rapid screening decisions, but also give eye-movement/attention information to higher echelons of care that may be helpful for any potential rehabilitation treatments on the brain-injured warfighter.

5. Conclusion

Traumatic brain injury, and especially mTBI, is an ongoing concern among the military medical community and operational commanders.

Premature RTD places warfighters at greater risk of short- and long-term disability if they suffer additional concussive brain trauma. Results of the present study indicate the KD test shows promise as an additional screening tool for mTBI. However, due to intrasubject performance variability that can impact subjective test results, we recommend the KD test be utilized as a supplementary screening tool in those who have suffered an mTBI event. In addition, having pre-injury KD data will allow a more precise determination; therefore, we recommend the KD test be included as a baseline test for all warfighters prior to exposure to risk of mTBI/concussion. Having a validated, rapid, easy-to-assess mTBI brain screening test can assist frontline providers in making the RTD decision to send the warfighter back to the "fight", or to a higher echelon of care for more comprehensive tests.

Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation. I, or any of the co-authors, have no conflict of interest to report.

Acknowledgement

This research was funded by the Military Operational Medicine Research Program of the U.S. Army Medical Research and Materiel Command (USAMRMC), and FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP) under contract No.

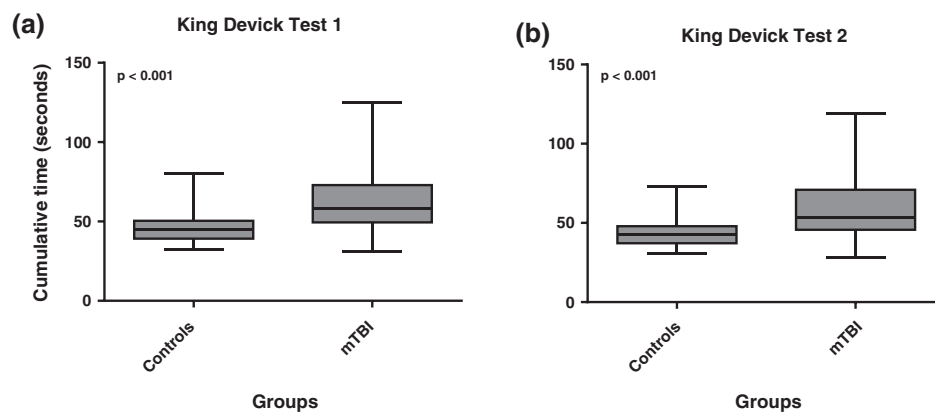


Fig. 3. Box- and-Whisker plots of (a) King-Devick test 1 controls and acute mTBI data and (b) King-Devick test 2 controls and acute mTBI data. The length of the box is the Interquartile Range (25–75%) with the middle line the median value of the data. The "whiskers" extending from the box represents the maximum and minimum range of the data. Significant differences between the controls and mTBI groups were seen in both test 1 and test 2 ($p < 0.001$).

W81XWH-14-C-0048. This research was conducted with support from the Geneva Foundation as well as the Defense and Veterans Brain Injury Center (DVBIC) and staffing support from General Dynamics Information Technology.

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APPENDIX I

Pages: 19
Words: 5,193
Tables: 5
Figures: 4
Appendices: 0
References: 32

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Validation of Visual Objective Biomarkers for Acute Concussion

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Keywords: pupillometer, pupillary light reflex, King-Devick Test, near point of convergence, convergence insufficiency symptoms surveys (CISS), mild Traumatic Brain Injury (mTBI), military, visual biomarkers

Presentations: Presented at the 2016 Military Health System Research Symposium, Kissimmee, FL, August 2016. (Abstract: MHSRS-16-0523).

Funding: This research was funded by the Military Operational Medicine Research Program of the US Army Medical Research and Materiel Command, and FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs under contract No. W81XWH-14-C-0048.

Disclaimer: The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

Abstract

OBJECTIVE: Despite an increase in the awareness and diagnosis of mild traumatic brain injury (mTBI) there remains a paucity of data examining the comparative efficacy of available assessments. This study aims to validate visual functions as potential biomarkers for mTBI.

METHODS: This case-control correlational design utilizes military personnel diagnosed with acute (≤ 72 hrs post-injury) mTBI ($n = 100$) and age-matched controls ($n = 100$) to examine the relative effectiveness of the pupillary light reflex (PLR), near point of convergence (NPC) break, King-Devick (KD) test, and Convergence Insufficiency Symptom Survey (CISS) to discriminate between participants with mTBI.

RESULTS: Three of the eight PLR parameters (i.e., average constriction velocity (ACV), average dilation velocity (ADV), 75% re-dilation time; all $p < 0.001$) were affected in mTBI participants. Similarly, NPC break, KD test, and CISS scores showed a statistically significant difference between groups (all $p < 0.001$). Area Under the Curve showed that ADV (.82) and NPC (.74) have the higher predictive values of all objective parameters.

CONCLUSIONS: ADV, ACV, and NPC break are objective visual functions markedly affected in the acute mTBI group compared to controls; therefore, we proposed they could be used as biomarkers for acute mTBI.

Introduction

Traumatic brain injury (TBI) is a significant public health issue in the United States. The Department of Defense reported 352,619 cases of clinically confirmed TBI from 2000 to the second quarter of 2016, with mild TBI (mTBI) accounting for 82.3 percent of all cases.¹ Similarly, the Centers for Disease Control and Prevention reported that TBI affects approximately 1.7 million people in the United States annually.² The total combined rates of TBI-related hospitalizations, emergency department visits, and deaths climbed from a rate of 521.0 per 100,000 in 2001 to a rate of 823.7 per 100,000 in 2010, with mTBI accounting for at least 75% of all TBIs in the United States.^{3,4} Unfortunately, mTBI continues to be a perennial challenge for the medical community primarily due to the lack of objective assessment tools.⁵ This challenge makes elucidating objective biomarkers of mTBI a top priority not only for providers but also for the patients they treat.^{5,6} Valid and objective biomarkers of acute mTBI are of particular importance in forward deployed situations for military clinicians to make accurate and immediate determination of return to duty (RTD) or evacuation for further evaluation.⁷

Visual processing and eye movements are frequently affected by mTBI. Common problems among patients presenting with mTBI include pupillary response deficit, visual processing delays (poor attention to detail, poor visual attention, and poor visual memory), photosensitivity, impaired oculomotor convergence (difficulty focusing on nearby objects or images), and related oculomotor-based reading dysfunctions. Given that approximately 30 areas of the brain and 7 of the 12 cranial nerves are utilized by the visual system, it is not unexpected that the patient with an injury to the brain typically presents with a variety visual problems. Sensory stimuli from the retinas are primarily routed to the visual cortex with numerous

connections in disparate areas among the frontal, parietal, and temporal lobes.⁸ The functional integrity of connections between these areas is vital for proper eye movement function and demonstrates the fragility of the visual system. Pathology at any point in the network risks disrupting the functional pathway thus producing errors or degrading performance.⁹ Therefore, tests involving the visual system are well suited for detecting the neurophysiologic effects of brain injury.¹⁰

The assessment of a patient's pupillary light reflex (PLR) is a long established and heavily relied upon indicator of neurological function in severely brain-injured patients.¹¹ The PLR refers to the involuntary response of the pupil that is evoked by an increase in illumination of the retina. The PLR however, is unique in that it is not under volitional control and therefore is unaffected by the motivation, effort, or bias from either the patient or the provider.

Initial studies in patients with repeated blast exposure have demonstrated the potential application of the PLR as an objective indicator and potential to aide in the diagnosis of mTBI. Advances in technology have significantly improved the accuracy and repeatability of automated infrared pupillometer allowing for more precise quantification of pupil dynamics.¹²⁻¹⁴ Two recently published studies evaluated PLR with a hand-held monocular pupillometer, NeuroOptics PLR-200™, as a potential objective test for subacute and chronic mTBI/concussions.^{15,16} Both studies showed significant differences between the control and mTBI groups on some of the eight data measurements provided by the pupillometer in relative small populations.

Due to the diffuse nature of typical mTBIs a wide range of vergence dysfunctions often manifest during the acute phase of injury.¹⁷ Another assessment used to evaluate potential brain trauma has been the presence of convergence insufficiency (CI). Neurological damage to the system that controls the muscles of the eyes may cause the image to fall on disparate locations on

the retina; this may manifest as blurred vision, double vision, fatigue, difficulty reading, or headaches. In multiple studies, CI has been shown to be commonly associated with brain injury.¹⁸⁻²⁰ CI is characterized by a receded near point of convergence (NPC). An NPC break beyond 10 cm is considered receded and indicative of convergence dysfunction.²¹ In addition to physical observation of CI, surveys have been developed for patient self-assessment of symptoms. The Convergence Insufficiency Symptom Survey (CISS) is a commonly used assessment for symptoms related to mTBI. The instrument has been validated and standardized for use in randomized clinical trials to subjectively measure the recovery of near vision symptoms in adults.^{18,22,23}

Lastly, tests involving the visual system which probe saccades and higher cortical functioning are well-suited for detecting the neurophysiologic effects of brain injury.¹⁰ Saccades refer to the quick, simultaneous movements of both eyes between two phases of fixation in the same direction. Among the more prominent and established assessments used in cases of suspected head trauma is the King-Devick (KD) test.²⁴ The KD test is designed to assess an individual's saccades and has demonstrated consistently high levels of test-retest reliability.²⁴⁻²⁶ KD test is subjective in nature; however, it has proven effective in identifying acute concussive athletes on the sidelines when compared to pre-injury baseline data.

The purpose of the present study is to validate PLR parameters and NPC break as objective biomarkers for acute mTBI, and to use them in combination with the KD test and CISS survey to increase their predictive power.

Methods

Subjects

Two hundred active duty service members seeking care at Womack Army Medical Center (WAMC) in Fort Bragg, NC were included in this study. One hundred participants with acute mTBI (≤ 72 hrs post-injury) were recruited at the Department of Brain Injury Medicine's Concussion Care Clinic and 100 age-matched controls were recruited while receiving routine care at the Department of Optometry. The diagnosis of mTBI was made by primary care providers based on the following criteria: loss of consciousness of no more than 30 min; posttraumatic amnesia of no more than 24 hours; any alteration of mental state; a Glasgow Coma Scale score from 13 to 15; and normal structural brain imaging. The study was approved by WAMC Institutional Review Board and the Human Research Protection Office of the US Army Medical Research and Materiel Command. Each subject provided written informed consent before participating in the study.

Pupillary Light Reflex

The PLR functions were measured with the NeuroOptics® PLR-200™ infrared pupillometer (Figure 1) as previously described.¹⁵ PLR was assessed under binocular conditions with dim illumination (~ 3 cd/ m²) while the subject fixated with the non-tested eye on a high-contrast target located at 3 m to avoid changes in pupil size due to accommodation. The PLR was recorded twice in each eye, alternating between eyes with an interval of no less than 45 seconds between the recordings. The eight PLR variables measured with the pupillometer were: 1) maximum diameter; 2) minimum diameter; 3) percent constriction; 4) constriction latency; 5) average constriction velocity (ACV); 6) maximum constriction velocity; 7) average dilation

velocity (ADV); 8) 75% re-dilation recovery time (T75). PLR administration took approximately 5 sec per eye.

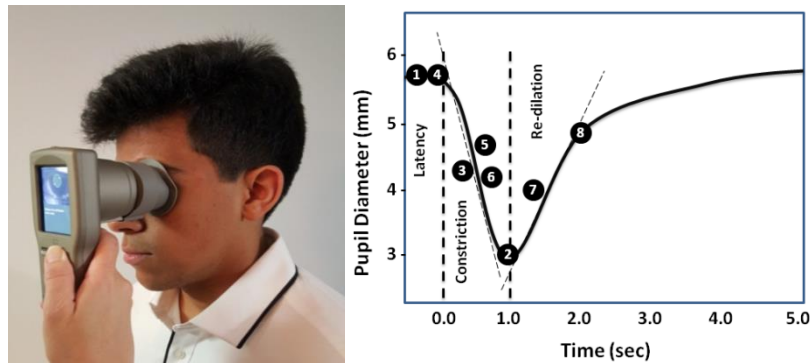


Figure 1. Left, demonstration of pupil assessment with PLR-200 monocular pupillometer. Right, schematic diagram of the typical pupillary reaction curve illustrating PLR recorded parameters: 1) maximum diameter; 2) minimum diameter; 3) percent of constriction; 4) constriction latency; 5) average constriction velocity; 6) maximum constriction velocity; 7) average dilation velocity; 8) 75% recovery time.

Near Point of Convergence

The objective break in NPC was measured using the Royal Air Force near point rule (Figure 2).

The Royal Air Force rule consists of a 50 cm long ruler with a slider holding a rotating four-sided rectangle. The test was administered in a well-lit room and participants were instructed to focus on a single high-contrast 20/30 size letter target. The examiner moved the slider with the accommodative target toward the subject's eyes and stopped when one of the eyes deviated out. If neither eye deviated, the NPC value was reported as "5" cm which reflects the minimum value on the convergence ruler. The distance (in cm) at which the eye deviated was recorded by noting the distance listed on the ruler. The break in NPC was measured twice with an approximately 5 minute interval between test administrations. Each NPC measure took approximately 10 sec.



Figure 2. Royal Air Force near point rule

King-Devick Test

The KD test was used to evaluate saccadic eye movement performance. The KD test involves reading aloud a series of single-digit numbers from left to right on three test cards (Figure 3). Standardized instructions provided with the instrument were used. The test was performed in a well-lit room at approximately a 40 cm reading distance. The participants were instructed to read the numbers aloud as fast as possible without making errors. If errors were made, the subject returned to correct the errors. The participants were instructed not to use their fingers on the card to assist during the testing. The cumulative time to read the three test cards were measured by the examiner using a stopwatch. The test was administered twice with an approximately five minute interval between test administrations. KD administration took between 30 to 120 sec.

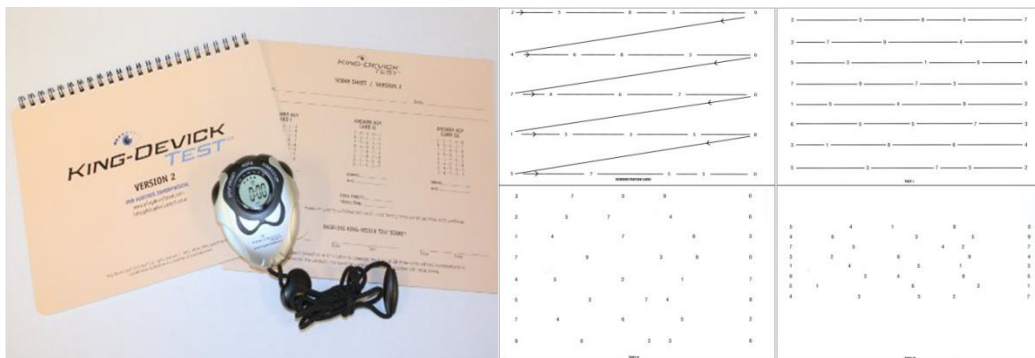


Figure 3. Left, King-Devick Test. Right, top left, Demo card; top right Test 1; lower left, Test 2; lower right, Test 3.

Convergence Insufficiency Symptoms Survey

The 15-question Convergence Insufficiency Symptoms Survey (CISS) was used to document symptoms associated with near visual tasks. Participants were asked to rate the 15 symptom questions on a five-point Likert-type scale. Each symptom question had five possible answers with an associated value, where 4 = always, 3 = frequently, 2 = sometimes, 1 = rarely, and 0 = never. Thus, the cumulative symptoms score can vary from 0 to 60. A healthy adult should score <21 points. The survey was completed only once and there was no time limit for this activity. PLR administration took between 60 and 120 sec.

Statistical Analysis

Demographic data, clinical characteristics, and assessment outcomes were assessed for normality using the Shapiro-Wilk test. The Kruskal-Wallis test was used to check for underlying demographic and clinical differences between the two groups as well as between the first and second trial. To assess the data for fatigue effects due to three assessments (PLR, NPC, and KD test) being conducted twice for each participant, Wilcoxon signed ranks tests were used to examine the significance of any differences between the first and second trial.

Receiver operating characteristic (ROC) curves were used to investigate the relationship between diagnostic sensitivity and specificity for two PLR parameters (ACV and ADV), NPC, KD test, and CISS. The area under the curve (AUC) was calculated for all significant objective and subjective predictors. Selecting instruments with an area AUC >0.60, a logistic regression analysis was performed. Based on the ROC AUC analysis, optimal cutoff values were determined for each significant predictor. Finally, a second regression analysis was performed using the identified cutoff values as predictors to determine the overall discriminate efficacy.

All data were analyzed by using IBM SPSS version 20 (IBM Corporation, Armonk NY, USA) and GraphPad Prism 6 (GraphPad Software, San Diego, CA). *P*-values < 0.05 were considered statistically significant. No cases with missing data were included in the analysis.

Results

Demographics & Mechanisms of Injury

A total of 224 patients were recruited for participation. Twenty-four participants were excluded from the acute phase mTBI group due to missing data. Consequently, 200 patients were included in the analyses and comprised the study sample of 100 participants with acute-phase mTBI and 100 age-matched controls.

Demographics information of both groups is shown in Table I. Data were included from 100 service members with acute mTBI (87 males, 13 females) and 100 age-matched controls (79 males, 21 females). The mean age was 26 ± 6 years and ranged from 19 to 44 years of age. No significant differences were found between the mTBI group and the age-matched controls on the basis of sex ($p = 0.13$) or race / ethnicity ($p = 0.70$). There was a significant difference in rank between the two groups ($p < 0.001$) with the mTBI group containing fewer officers than were present in the control group. Additionally, differences were observed in the distribution of eye color ($p = 0.01$). The mTBI group contained fewer individuals with blue eyes than were present in the control group. Neither of these was considered to be a relevant factor relating to mTBI and thus neither was included as a predictor in later regression analyses.

Table 1. Participant Demographics and Characteristics

Characteristic	Control n (%)	mTBI n (%)	p Value
Age, yrs			
18-22	29 (50.0)	29 (50.0)	1.00
23-27	40 (50.0)	40 (50.0)	
28-32	17 (50.0)	17 (50.0)	
33+	14 (50.0)	14 (50.0)	
Sex			
Male	79 (47.6)	87 (52.4)	0.13
Female	21 (61.8)	13 (38.2)	
Race / Ethnicity			
White	58 (49.2)	60 (50.8)	0.70
Black	18 (56.2)	14 (43.8)	
Hispanic	13 (48.1)	14 (51.9)	
Asian	6 (66.7)	3 (33.3)	
Other	5 (35.7)	9 (64.3)	
Rank			
Junior Enlisted (E1-E3)	25 (58.1)	18 (41.9)	< 0.001*
NCO (E4-E8)	50 (40.3)	74 (59.7)	
Officer (O1-O5)	25 (75.8)	8 (24.2)	
Eye Color			
Light Brown	9 (45.0)	11 (55.0)	0.01*
Brown	47 (43.1)	62 (56.9)	
Green	11 (52.4)	10 (47.6)	
Blue	33 (66.0)	17 (34.0)	

* Statistically significant ($p \leq 0.05$)

To qualify for participation individuals in the mTBI group must have been in the acute phase of injury (≤ 72 hours post-injury). Thirty one percent of the mTBI group presented to the clinic within 24 hrs, 40% presented within 48 hrs, and 29% presented within 72 hrs. The most common mechanism of injury was airborne training activities (jump), 69%. The remaining injuries were attributed to fall (7%), motor vehicle accident (6%), other (6%), blunt force (5%), sports/recreation (5%), and combative training (2%).

Among the mTBI group, current medications were evaluated for potential confounding effects on pupillary dynamics. Of specific interest were mydriatic drugs and amphetamines,

which may artificially dilate the pupils; anticholinergics that may impede normal constriction and dilation; and opiates which may lead to artificial pupillary miosis (constriction). None of the medications prescribed to the participants in the mTBI group were considered to potentially affect the PLR measures. The most common medication used by participants was acetaminophen ($n = 26$) followed by ibuprofen ($n = 25$).

To further confirm that undisclosed medications were not significantly affecting pupillary dynamics in the either group, the latency and maximum pupillary dilations were examined. The mean latency between light stimulus and pupillary constriction was 215.85 ± 22.17 ms for the right eye and 213.80 ± 22.45 ms for the left eye as measured by the PLR-200. These results were in accordance with previous research,^{27,28} which indicates latencies between 200 and 450 ms are indicative of normal pupillary function. To confirm age related decline in pupil size, Spearman correlations were produced for age and maximum pupil diameter. Both, the right and left eyes were significantly correlated with age ($r = -0.31$, $n = 100$, $p = 0.002$ and $r = -0.38$, $n = 100$, $p < 0.001$, respectively).^{27,28}

Pupillary Light Reflex

There was no statistically significant difference (all $p > 0.05$) for any of the PLR parameters between the right and left eye nor between trials. Therefore, PLR data from trial 1 and 2 for the right and left eye were combined for further between-group comparison. Results indicate that three of the eight PLR parameters are suited to objectively differentiating between normal and mTBI participants (Table 2). The ACV and ADV were slower in the mTBI group ($p < 0.001$, $\eta^2 = 0.07$; and $p < 0.001$, $\eta^2 = 0.30$, respectively). In addition, it took longer for pupils

to reach 75% of pre-stimulated size among the acute mTBI group compare to controls, $p < 0.001$, $\eta^2 = 0.30$.

Table 2. Summary Statistics for PLR Parameters^a

Variable	Group	N	Mean	Std. Deviation	95% Confidence Interval		p Value
Maximum Diameter (mm)	Control	100	5.97	0.73	5.83	6.12	0.14
	mTBI	100	5.74	0.97	5.56	5.94	
Minimum Diameter (mm)	Control	100	4.00	0.61	3.89	4.13	0.19
	mTBI	100	3.87	0.64	3.73	4.03	
Percent Constriction (%)	Control	100	33.19	3.87	32.40	33.98	0.45
	mTBI	100	32.69	4.54	31.79	33.57	
Constriction Latency (msec)	Control	100	218.93	18.00	215.50	222.61	0.18
	mTBI	100	214.83	19.56	211.08	218.61	
Average Constriction Velocity (mm/sec)	Control	100	4.05	0.53	3.95	4.16	<0.001*
	mTBI	100	3.65	0.76	3.50	3.81	
Maximum Constriction Velocity (mm/sec)	Control	100	5.31	0.67	5.18	5.46	0.69
	mTBI	100	5.24	0.78	5.08	5.39	
Average Dilation Velocity (mm/sec)	Control	100	0.94	0.19	0.90	0.98	<0.001*
	mTBI	100	0.62	0.27	0.56	0.66	
75% Recovery Time (sec)	Control	100	2.60	0.60	2.47	2.71	<0.001*
	mTBI	100	4.00	1.09	3.78	4.22	

^a Results based on mean of two trials; * Statistically significant ($p \leq 0.05$)

Near Point of Convergence

The mean NPC break for the acute mTBI group 13.25 ± 8.07 cm and for the controls was 8.18 ± 2.15 cm. Statistically significant results indicate that the acute mTBI group had receded NPC compared to controls, $p < 0.001$ (Table 3). Based on the guideline that scores greater than 10 cm indicated receded convergence, the sensitivity and specificity of the NPC break were 0.81 and 0.49, respectively. This indicates a high number of false positives (51%).

King-Devick Test

The mean KD completion time for participants in the acute mTBI group was 60.28 ± 19.50 sec and the mean KD completion time for controls was 44.53 ± 8.05 sec. Statistically significant results indicate that the acute mTBI group took longer to complete the KD test $p < 0.001$ (Table 3). Based on K-D test guidelines for injury determination the sensitivity and specificity of the KD test were 0.45 and 0.92, respectively. This indicates a high number of false negatives (55%).

Table 3. Summary Statistics for NPC, KD test and CISS

Variable		N	Mean	Std. Deviation	95% Confidence Interval		p Value
					Lower Bound	Upper Bound	
NPC Break (cm)	Control	100	8.18	2.15	7.75	8.6	< 0.001*
	mTBI	100	13.24	8.07	11.64	14.84	
KD Test (sec)	Control	100	44.53	8.05	42.93	46.12	< 0.001*
	mTBI	100	60.28	19.5	56.41	64.15	
CISS Score	Control	100	8.82	7.42	7.35	10.29	< 0.001*
	mTBI	100	24.76	12.06	22.37	27.15	

Convergence Insufficiency Symptoms Survey

The mean CISS score was 24.76 ± 12.06 among participants in the acute phase mTBI group and 8.82 ± 7.42 for the controls. Results indicate that the higher CISS scores for the acute phase mTBI group represent a statistically significant difference, $p < 0.001$ (Table 3). Using the cutoff score of 20, the sensitivity and specificity of the CISS were 0.59 and 0.91, respectively. The number of false negatives among the acute mTBI participants closely mirrors the results of the KD test.

Area Under the Curve (AUC)

The AUC was calculated for two of the PLR measures (ACV and ADV) as well as for the NPC, KD test, and CISS. Although T75 was statistically different between the groups, it was not included within the ROC analysis since it is dependent on dilation velocity. Table 4 shows that ADV (.82) and NPC (.74) have the higher predictive values of all objective parameters.

However, the highest predictable values of all parameters were subjective in nature: CISS (0.86) and KD test (0.78). Figure 4 depicts the ROC curves for all significant variables. Using their respective ROC curves, cutoff scores for ADV, KD test, and CISS score were determined to be 0.84 mm/sec, 47 sec, and 14 respectively.

Table 4. Area under the curve (AUC) values for all statistically significant variables

Variable	AUC	SD	95% Confidence Interval	
			Lower Bound	Upper Bound
Average Dilation Velocity	0.815	0.030	0.756	0.874
Average Constriction Velocity	0.650	0.039	0.574	0.725
Near Point Convergence	0.744	0.034	0.676	0.811
King-Devick Test	0.777	0.033	0.711	0.842
Convergence Insufficiency Symptom Survey	0.860	0.027	0.808	0.912

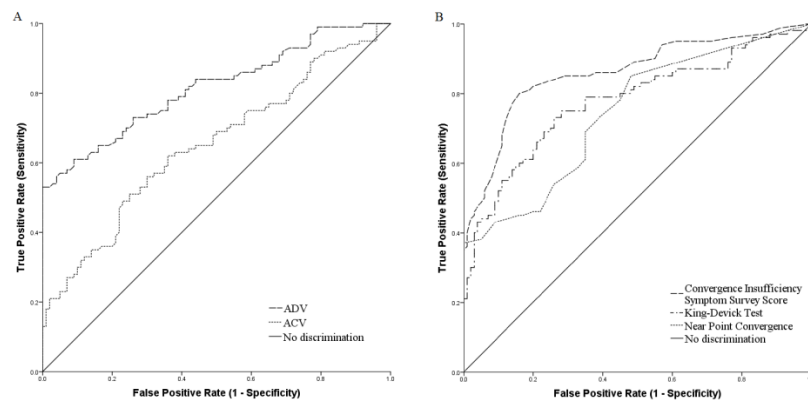


Figure 4. Receiver operating characteristic (ROC) curves showing the diagnostic performance for (A) PLR parameters: ADV and ACV; (B) Other assessments: CISS, King-Devick test, NPC.

Regression Analysis

Binary logistic regression was used to predict injury status (acute phase mTBI or control) using participant's scores on the KD test, NPC, CISS, and PLR parameters (ADV and ACV). A test of the full model was statistically significant, indicating that the predictor variables reliably discriminated between the groups ($p < 0.001$). The resulting Nagelkerke R^2 of 0.71 indicates a moderately strong relationship between the predictor variables and the group variable.

Prediction success overall was 87.5% (91.0% for controls and 84.0% for acute phase mTBI participants). Regression coefficients are presented in Table 5. ROC curve analysis indicates an AUC for the model of 0.93 which indicates very good overall accuracy for the model.

Table 5. Regression Coefficients

Predictor	<i>B</i>	S.E.	<i>Wald</i>	<i>df</i>	<i>p</i>	OR	95% Confidence Interval	
							Lower Bound	Upper Bound
ACV	5.54	4.72	1.38	1	0.24			
ADV	3.35	0.84	16.07	1	<0.001	28.61	5.55	147.48
KD Test	0.06	0.03	5.39	1	0.02	1.06	1.01	1.11
NPC	-0.01	0.08	0.02	1	0.88			
CISS	0.13	0.03	22.83	1	< 0.001	1.14	1.08	1.20
Constant	-10.46	1.88	30.91	1	< 0.001	0.00		

ACV = average constriction velocity; ADV = average dilation velocity; KD = King-Devick; NPC = near point of convergence; CISS = Convergence Insufficiency Symptom Survey; S.E. = Standard Error; OR = odds ratio; * Statistically significant ($p \leq 0.05$)

Finally, a second binary logistic regression was used to predict injury status (acute phase mTBI or control) using previously determined cutoff scores for the KD test, CISS, and ADV. A test of the full model was statistically significant, indicating that the predictor variables reliably discriminated between the groups ($p < 0.001$) with a Nagelkerke R^2 of 0.61. Prediction success

overall was 84.0% (86.0% for controls and 82.0% for acute phase mTBI participants). ROC curve analysis of the model indicates an AUC of 0.90 which indicates very good overall accuracy for the model.

Discussion

Cognitive and neurosensory degradation resulting from mTBI is significant to each patient, but is of unique concern among military service members. Peak cognitive and physical performance is often crucial for military personnel as lives may depend on their ability to perform both physically and cognitively. Due to the relatively mild symptomology and transient nature of the injury, service members are frequently returned to full duty within 24 hours. However, misdiagnosis or premature RTD potentially places service members at greater safety risks as well as increase chance for long term disabilities should they suffer further concussive events before complete recovery.²⁹ This sometimes premature discharge risks exposing service members to repeat injuries with possible long term consequences. Consequently, a quick and accurate diagnosis of mTBI could result in increased safety for others as well as a better prognosis for the individual.³⁰

The present study validated the use of the PLR (i.e., ACV and ADV) and NPC break as objective biomarkers for acute mTBI. These visual functions can be accurately and quickly measured using instrumentation that is portable, non-invasive, causes no discomfort or risk to patient, minimal training, deployable, commercially available, and relatively low cost. Objective biomarkers, such as these visual function assessment, are needed to assist front-line medical providers in making RTD decisions after a suspected acute mTBI.

However, given the variety of visual deficits resulting from mTBI and the broad range of injury severity within the mTBI category, it is unrealistic to expect that a single visual function can serve as a universal concussion biomarker. This study shows that a combination of visual functions increases the sensitivity to correctly identify acute mTBI than any one test alone. Results of the present study indicate that the ADV and ACV of the PLR are better suited for discriminating between individuals with and without acute phase mTBI than other commonly used instruments. The PLR re-dilation deficit demonstrated in acute-phase mTBI patients is not surprising given the diffuse nature of vision in neural structures. This is in agreement with two previous studies evaluating PLR using the same device, but in blast-induced subacute military¹⁵ and non-blast chronic civilian populations with mTBI.¹⁶ Both of these studies were performed in relatively small population of mTBI subjects (≤ 20). The autonomic nervous system governs the process of pupil dilation and constriction. Previous research has hypothesized that mTBI related PLR deficits may result from disequilibrium in the autonomic nervous systems due to diffuse injury or transient neuroendocrine dysfunction.¹⁵

While the exact neurocognitive mechanism(s) affecting individuals with acute mTBI are unclear, it is clear that new objective diagnostic techniques are needed for screening mTBIs. The standard penlight technique of assessing visual function lacks the objective precision needed to inform such a crucial decision as RTD or return to play. While all the measures used in this study are established as objective measures, only the PLR is truly free from patient and provider bias. Thus, assessment of the PLR represents a quick, non-invasive, and objective method by which disruptions to the autonomic nervous systems such as acute mTBI may be identified.

Previous studies have validated the use of screening instruments such as the KD test, though often among athletes who also received baseline assessments for comparison. Research

done without the use of baseline assessments has been more mixed. A study of acute phase mTBI patients presenting to an emergency department failed to find significant differences in KD test performance, potentially due to small sample size.³¹ A more recent study in a larger population showed the benefit of KD test as an acute mTBI screening tool in the absence of a baseline score,³² particularly when used in conjunction with other objective screening tools. In addition, the CISS score increase observed in the present study is also in agreement with a previous study examining military personnel diagnosed with blast-induced subacute mTBI.²²

Therefore, whether in a warzone, training environment, or sports field, results suggest that assessment of the PLR is the most effective method of screening for acute phase mTBI. Incorporating an assessment of the PLR into mTBI screening protocols may improve the accuracy of injury assessments not only in a military setting but also in sports and emergency care situations. This may result in a reduction of false-negatives, thereby allowing affected individuals to recover rather than continuing activities and risking exacerbating the injury. Lastly, these results may assist with the development of a weighted neuropsychometric testing battery for the diagnosis of acute mTBI.

Several limitations to the study were identified and should be considered when evaluating the results. The participants were convenience sampled from clinics in a military setting. Therefore, the data cannot be assumed to be representative of the greater civilian population given differences in age, gender distribution, and fitness level. In addition, the majority of acute phase mTBI participants in this study suffered injury after jumping from an airplane, a mechanism of injury not likely to be the primary cause of mTBI in the civilian population. However, this injury modality still represents blunt force trauma to the head and diagnostic criteria for mTBI were similar to those used in civilian populations. Additionally, none of the

acute phase mTBI injuries resulted from blast exposure. Consequently, the results of this study cannot be assumed to hold for samples of individuals with blast injuries or polytrauma such as may occur in motor vehicle accidents or assaults. Finally, the instruments used in this study have been demonstrated to be effective screening tools for mTBI during the acute injury phase. However, the ability to assess the severity of injury or provide prognosis information was not evaluated. Thus, while the results of this study can inform injury evaluation in general, no claim can be made regarding the clinical utility of these screening tools for determining injury severity or likely persistence of symptoms and recovery times.

Conclusion

Our findings demonstrate that ADV, ACV, and NPC break are objective visual functions markedly affected in the acute mTBI group compared to controls, and therefore, appear to be useful biomarkers for acute mTBI. The study results also support the added benefit of using vision related subjective instruments, such as the KD test and CISS, in conjunction to abovementioned objective biomarkers, to increase the predictability to identify acute mTBI. Thus, while each instrument can accurately differentiate the injury and control groups, results suggest that they differ with regard to their sensitivity and specificity. Where available, objective assessment (i.e., ADV, ACV, and NPC) should be considered preferable to subjective assessments and those based on self-report. Healthcare providers should consider the relative differences of available assessment tools when screening for acute mTBI and consider the use of multiple assessments when feasible to aide in making RTD and return to play determinations or to monitor the recovery of post-concussive syndrome.

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Pages: 13

Words: 1,716

Tables: 3

Figures: 0

References: 15

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Assessment of the NPi-100 Pupillometer test for screening acute mTBI/concussion in Warfighters

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Abstract

OBJECTIVES: The Department of Defense reported that 357,048 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to the third quarter of 2016, with mild TBI (mTBI) accounting for 82.3 % of all cases. Unfortunately, Warfighters with TBI are often identified only when moderate or severe head injuries have occurred, leaving more subtle mTBI cases undiagnosed. This study aims to validate an automated monocular pupillometer for screening acute mTBI.

METHODS: Two-hundred active duty subjects were recruited to assess the mTBI screening effectiveness of the NeurOptics® NPi™ -100 (NPi-100) pupillometer. Two-hundred subjects were equally divided into two groups; those with diagnosed acute mTBI (≤ 72 hrs) and age-matched controls. Eight outcome measures were collected by the pupillometer with the primary outcome measure being the neuro-pupillary index (NPi).

RESULTS: In both eyes, significant differences were seen between the two groups with three of the eight outcome measures; average constriction velocity (OD/OS: $p < 0.001$), maximum constriction velocity (OD/OS: $p < 0.001$), and average dilation velocity (OD: $p = 0.002$, OS: $p < 0.001$). However, significant differences between the mTBI and control groups were not seen with the primary outcome measure of NPi value.

CONCLUSIONS: In both eyes, significant differences between the acute mTBI and control groups were found in ~ 40 % of the eight outcome measures. However, no significant differences were observed with the primary outcome measure of NPi. This lack of significant differences may be due to the NPi algorithm being unequally weighted or the mild neurological sequela of mTBI may not be a sensitive biomarker for screening mTBI with the NPi value.

Keywords: NPi-100 Pupillometer, Neuro-Pupillary index (NPi), mild traumatic brain injury (mTBI), military

1. Introduction

The Department of Defense reported that 357,048 cases of traumatic brain injury (TBI) were clinically confirmed from 2000 to the third quarter of 2016; with mild TBI (mTBI) accounting for 82.3 percent of all cases (1) . Warfighters with mTBI can be more difficult to diagnose versus those warfighters who have suffered moderate to severe TBI due to the overlap of co-morbid disorders such as post-traumatic stress disorder, and the difficulty in diagnosing self-reported brain injury/concussion symptoms to the health provider (11, 12).

A 2010 military mTBI diagnostics workshop highlighted the importance of finding biomarker or diagnostic tests to expedite the diagnosis of warfighters suspected of having a concussion/mTBI (7, 12). Undiagnosed mTBI/concussions can put lives and safety in danger, and expose injured warfighters to the potential effects of further concussions/brain injuries which have shown to have additive detrimental effects (13). The identification of a rapid, easy to interpret, objective diagnostic test can assist front-line providers/medics in making Return-to-Duty (RTD) decisions in suspected brain injured warfighters.

The pupil examination is the foundation for neurological assessments by healthcare providers and usually relies on the manual "swinging flashlight" pupillary assessment with a penlight. However, the manual pupillary assessment is highly subjective and does not provide the level of accuracy necessary to detect subtle pupillary deficits (6, 8, 15). Advances in technology have significantly improved the accuracy and repeatability of automated infrared pupillometer allowing for more precise quantification of pupil dynamics (5, 8). Two recently published studies

evaluated the pupillary light reflex (PLR) with a hand-held monocular pupillometer, NeuroOptics PLR-200™, as a potential objective biomarker test for mTBI/concussions (2, 14). Both studies showed significant differences between the control and mTBI groups on some of the eight data measurements provided by the instrument. However, the PLR-200 has two concerns that limit its usefulness as a RTD screening test. First, there is no normative database embedded into the PLR-200 to act as “controls” in comparing data provided by the potentially brain-injured warfighter. Second, the PLR-200 does not provide easy to interpret composite value that a front-line provider/medic would require in making rapid RTD decisions. Unlike the PLR-200, the NeuroOptics® NPi™ -100 (NPi-100) pupillometer has a normative database embedded into the instrument and has a unique data point called the Neuro-Pupillary index (NPi). The NPi is based off an algorithm that takes some of the remaining variables inputs and compares them to the normative database to give a composite score pupillary response between 0-5; a value below 3 is considered an abnormal pupillary reflex (9). The NPi could serve as an objective and quantifiable value that can be trended over time and has shown promising results in usage in Critical and Neuro-Intensive Care Units (3, 4, 10). Though the NPi has shown promise in monitoring recovery of patients with severe conditions, its usefulness has not been tested in more subtle injuries such as mTBI/concussion.

The purpose of this study was to evaluate the effectiveness of the NPi value of the NPi-100 pupillometer to serve as an objective biomarker to identify warfighters diagnosed with acute mTBI/concussion. If the NPi-100 is validated, this could lead to decision makers equipping front-line providers/or medics with an easy to administer, quick to assess, objective test that can assist the provider/medic in making RTD decisions of sending an injured warfighter back to a higher echelon of care, or back to combat.

2. Methods

2.1. Subjects

Two-hundred active duty military personnel were recruited for the study. One hundred participants with acute mTBI (≤ 72 hrs post-injury) were recruited at the Department of Brain Injury Medicine's Concussion Care Clinic and 100 age-matched controls were recruited while receiving routine care at the Department of Optometry. Though a normative database is embedded into the NPi-100 pupillometer, no statistical p -values are included with the outcome measurement data. Therefore, age-matched control data was collected to make statistical comparisons in the eight outcome measures between the two groups.

The diagnosis of mTBI was made by primary care providers at a military Concussion Care Clinic based on the following criteria: loss of consciousness of no more than 30 min; posttraumatic amnesia of no more than 24 hours; any alteration of mental state; a Glasgow Coma Scale score from 13 to 15; and normal structural brain imaging. Inclusion criteria for the control group were any active duty service member with no history of mTBI/concussion. The study was approved by the Womack Army Medical Center Institutional Review Board and the US Army Medical Research and Materiel Command, Human Research Protection Office. Each subject provided written informed consent before participating in the study.

2.2. Equipment & Procedures

The PLR functions were measured with the NeuroOptics® NPi™-100 (**Fig. 1**). The test was administered under dim illumination (~ 3 cd/ m²) under binocular conditions. The tester positioned the pupillometer at a right angle to the subject's axis of vision as the measurement was taken. The subject was instructed to fixate with the non-tested eye on a distance target located at 10 feet away to avoid changes in pupil size due to accommodation and to prevent

recording artifacts by blinking during PLR recordings. The PLR was recorded twice in each eye, alternating between eyes with an interval of no less than 45 seconds between the recordings. The eight PLR variables measured with the NPi-100 pupillometer were: 1) maximum diameter; 2) minimum diameter; 3) percent of constriction; 4) constriction latency; 5) average constriction velocity; 6) maximum constriction velocity; 7) average dilation velocity; 8) NPi.



Figure 1. NPi-100 monocular pupillometer

2.3. Statistical Analysis

Shapiro-Wilk tests for normality was performed and to compare the group's performance, a Mann-Whitney U was performed on non-normal distributions and an independent *t*-test on normally distributed data. All significance levels were $p < 0.05$, and statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 20.0 software and GraphPad Prism 6 (GraphPad Software, San Diego, CA).

3. Results

3.1. Demographics & Mechanisms of Injury

Demographics information of both groups is shown in **Table 1**. The mean age of both groups was 26.31 ± 5.83 yrs. In both groups, males were predominantly the subjects (87% mTBI vs.

79% controls), and most were junior enlisted (E1-E-4), Caucasian, Army soldiers. The Mechanisms of Injury (MOI) of the acute mTBI group are shown in **Table 2**. Out of the 100 mTBI subjects, a 69% had a parachute jump resulting in a concussion. Each of the remaining mechanisms of injury reported (blunt force, combative, fall, motor vehicle accident, sports/recreational activities, other) had a less than 10% injury cause rate.

Table 1. Demographics

	mTBI (n = 100)	Controls (n = 100)
Age (years \pm SD)	26.31 \pm 5.83	26.31 \pm 5.83
Gender (%)		
<i>Males</i>	87	79
<i>Females</i>	13	21
Branch (%)		
<i>Army</i>	99	97
<i>Marines</i>	1	0
<i>Navy</i>	0	1
<i>Air Force</i>	0	2
Military Rank (%)		
<i>E1-E4</i>	62	54
<i>E5-E6</i>	25	17
<i>E-7-E9</i>	3	2
<i>CW2-CW3</i>	2	2
<i>O1-O5</i>	8	25
Ethnicity (%)		
<i>Caucasian</i>	60	58
<i>African- American</i>	14	18
<i>American-Indian</i>	3	1
<i>Hispanic</i>	14	13
<i>Asian</i>	3	6
<i>Other</i>	6	4

SD = Standard Deviation

Table 2. Mechanisms of Injury

	Percent (%)
Blunt Force	5
Combative Training	2
Fall	7
Parachute Jump	69
Motor Vehicle Accident	6
Sports/Recreational Activities	5
Other	6

3.2. NPi-100 results

Results of the between-group analyses of NPi-100 outcome measures shown in **Table 3**. In both eyes, three of the eight outcome measures showed significant differences between the two groups (average constriction velocity (OD: $t(198) = 4.01, p < 0.001$; OS: $t(198) = 4.14, p < 0.001$), maximum constriction velocity (OD: $U = 3604, p < 0.001$; OS: $U = 3554, p < 0.001$), and average dilation velocity (OD: $t(198) = 3.08, p = 0.002$; OS: $t(198) = 3.54, p < 0.001$). In the OD only, percent constriction was significant between the groups ($t(198) = 2.53, p = 0.01$). The primary outcome measure of NPi value was not significant between the groups in either eye.

Table 3. NPi-100 pupillometer between-groups comparisons

NPi 100 measure	mTBI	Controls		mTBI	Controls	
	OD	OD	<i>P</i>	OS	OS	<i>P</i>
†Maximum Diameter (mm)	5.99 (5.19-6.41)	5.92 (5.22 – 6.61)	0.76	5.91 (5.26 – 6.55)	5.78 (5.26 – 6.41)	0.74
†Minimum Diameter (mm)	3.56 (3.10 – 3.93)	3.41 (3.02 – 3.91)	0.55	3.46 (3.03 – 3.94)	3.44 (3.03 – 3.78)	0.68
††Percent Constriction (%)	39.31 ± 4.90	40.88 ± 3.82	0.01*	39.51 ± 5.13	40.45 ± 3.72	0.14
†Constriction Latency (ms)	220 (220- 235)	220 (220 – 220)	0.08	220 (205 – 235)	220 (205 – 235)	0.74
††Ave Constriction Velocity (mm/sec)	3.08 ± 0.57	3.38 ± 0.46	<0.001*	3.11 ± 0.57	3.42 ± 0.49	<0.001*
†Maximum Constriction Velocity (mm/sec)	5.16 (4.64-5.56)	5.49 (4.99 – 6.00)	<0.001*	5.20 (4.73-5.73)	5.60 (5.06 – 6.13)	<0.001*
††Ave Dilation Velocity (mm/sec)	1.24 ± 0.28	1.37 ± 0.31	0.002*	1.30 ± 0.30	1.44 ± 0.26	<0.001*
†NPi value	4.40 (4.20 – 4.50)	4.50 (4.30 – 4.60)	0.08	4.40 (4.30 – 4.60)	4.40 (4.20 – 4.58)	0.79

Note: †=Median/Interquartile range reported; ††= Mean/ Standard deviation reported; **p* < 0.05 (shaded area)

4. Discussion

The primary aim of the present study was to investigate the potential implementation of an easy to administer, and quick to interpret automated pupillary light reflex test (NeuroOptics® NPi™ - 100) in assessing warfighters who were diagnosed with acute mTBI/concussion. Results from the study demonstrated significant differences in ~ 40% of the outcomes measures between the acute mTBI and age-matched control groups. However, significant differences between the two study groups were not observed with the primary outcome measure of NPi value. We believe this is the first study to evaluate the potential viability of the NPi as an objective biomarker value in mTBI subjects.

Previous studies using the NPi-100 pupillometer on non-mTBI patients/subjects that focused on the application of the NPi have shown promising results. In a 2011 study, Chen et al., found in patients with Increased Cranial Pressure (ICP) due to severe TBI, aneurysmal subarachnoid hemorrhage, or spontaneous intracerebral hemorrhage the NPi had an inverse relationship with ICP and concluded the NPi could be used as a management tool in intensive care units (3). In a retrospective chart review of five TBI patients, Chen, et al., found the NPi scores could be, “a component of the clinical exam, provide a sensitive, noninvasive and quantitative means of following pupillary function acutely and chronically after a traumatic brain injury”(4). Finally, in a recent study the NPi score, was found to have good correlation with a Glasgow Coma Score < 9 and ICP > 30 H₂O; however, the correlation was weaker with ICPs below 30 H₂O (10). The key difference in all the previous studies on NPi viability versus the present study were the etiologies/types of conditions in the former studies were more severe than those seen in the present study.

The lack of NPi value significance between the two study groups in the present study may be due to two reasons. First, the algorithm to determine the NPi is based on the results of some of the remaining seven outcome measures. This algorithm may be unequally weighted among the outcome measures, and thus the measures not significant between the two study groups may have a higher “weight” in determining the NPi. The algorithm used by Neuroptics is proprietary therefore the exact PLR parameters and individual weight taken in consideration is known. Second, the mild sequelae of mTBI may not produce as much an effect on the NPi as seen in more severe cases of neurological insult that were noted in the previous studies with the NPi-100 pupillometer.

5. Conclusion

Traumatic Brain Injury, with mTBI being the common classification, is an ongoing concern among the military medical community and operational commanders. Results of the present study indicated that though some of the NPi-100 pupillometer outcome measures were significant between both groups, the main outcome measure of NPi was not effective as a biomarker screening parameter. Further advancements in pupillometer technology could produce an easy to administer and interpret value to help the front-line medics/frontline providers make RTD decisions in sending the warfighter forward to the “fight,” or back to a higher echelon of care for more comprehensive testing.

Acknowledgement

This research was funded by the Military Operational Medicine Research Program of the US Army Medical Research and Materiel Command (USAMRMC), and FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP) under contract No. W81XWH-14-C-0048. This research was conducted with support from the Geneva Foundation as well as the Defense and Veterans Brain Injury Center (DVBIC) and staffing support from General Dynamics Information Technology.

Disclaimer

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